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News of Individual Bulletins

Therapeutics Initiative, Canada: Funding Issues

Ciprian Jauca

In April 2012, the budget of the Therapeutics Initiative program was cut by the British Columbia Ministry of Health by 45%. Then in July 2012, as a result of an internal investigation into alleged unspecified inappropriate data access within the Ministry, the Ministry of Health suspended Therapeutics Initiative's access to de-identified Pharmanet (dispensed prescriptions) and other administrative databases (vital statistics, medical treatments, diagnostic tests, hospitalisation).

In September 2012, the Therapeutics Initiative was informed that its operating grant from the government was suspended. Despite this, the Therapeutics Initiative has continued the work that is not dependent on data access, and the reduced funding has continued.

As a result of these disruptions, the Therapeutics Initiative is currently in a 'holding pattern', with the main objective of maintaining its core academic and support staff in the hope that its situation improves.

Contents

Dialogo sui Farmaci, Italy: Funding Issues

Maria Font

Until 31 December 2012, Dialogo sui Farmaci (DsF) was the most widely disseminated independent bulletin in Italy. Every year it was distributed to nearly 7 000 readers mainly in the Veneto Region.

DsF was published by a public limited liability company (LLC) that was jointly owned by two institutions belonging to the Italian National Health Service: the University Hospital and the Local Health Unit of Verona. The bulletin was produced by six staff employed by the LLC as well as some external contributors most of whom work in the Local Health Unit of Verona. The majority of the funding for DsF (88% of its budget) was derived from subscription revenue, but a small portion (12% of its budget) came from public funds of the Veneto Region. This public funding had been progressively cut in the last two years.

In 2012 the Italian Government decided that all public companies should be dissolved to reduce public expenditure. So the University Hospital and the Local Health Unit of Verona disbanded the LLC at the end of 2012 and publication of DsF came to a halt after 22 years.

The Editorial board of DsF asked the Veneto Region to support an electronic version of the bulletin with the inherent savings on production and dissemination costs. Despite numerous support letters from readers, contributors, ISDB and many others who valued the information produced by DsF, the administrators of the Veneto Region refused to keep the bulletin going. All six editorial staff members were offered a one-year contract to work on different regional projects. Of these, four accepted the proposal.

Meanwhile, three different private editors have expressed an interest in purchasing the LLC and publishing DsF but without any assurances regarding the quality of content and the independence of the bulletin. In the next few weeks the administrators of the Local Health Unit of Verona will make a decision about the future of DsF.

Other Italian independent drug bulletins are also facing crises as subscribers' fees are not sufficient to fully fund independent drug bulletins. It is clear that public institutions do not intend to support independent bulletins or take on their role. Our major concern is that pharmaceutical companies will be the sole source of information for Italian prescribers.

Postscript

The Local Health Unit of Verona has recently given approval for the continuation of information activities and publication of an electronic bulletin named Infofarma. The main traits of DsF will be preserved in this new e-bulletin, which will be launched on the website in a few weeks time.

Anahit Ayvazian, Armenia (l) and Natalia Cebotarenco, Moldova (r). Missing are people from Kazakhstan and Ukraine.

Bulletin MEDEX, Moldova: A Conversation

Natalia Cebotarenco

Why was your bulletin started?

After *perestroika* many new and unknown medicines were introduced into the former Soviet Union but there was no accompanying information in Russian or the local languages. Nor was there a source of independent drug information so healthcare authorities, physicians, and pharmacists did not know how to use these medicines.

I taught clinical pharmacology in the university faculties of medical and pharmacy, and with my colleagues, we started MEDEX to provide a source of independent drug information in Moldova for health workers.

How long has your bulletin been going, how often do you publish it and who receives it?

The bulletin MEDEX was started in January 1996 and is now published four times a year. The bulletin is distributed electronically – not only in Moldova but also in other Russian-speaking countries. Our bulletin is the only source of independent drug information in Moldova. Our readers are doctors, pharmacists, medical students and healthcare authorities.

What resources do you have to produce the bulletin?

The editorial team is small: physicians and pharmacists from Moldova, Armenia, Kazakhstan and Ukraine. The editorial team works on a voluntary basis.

Do you liaise with other like-minded organisations in your area?

There are no similar organisations in Moldova, but thanks to the Internet we are able to collaborate with colleagues from other countries.

What kind of issues do you cover in your bulletin?

We try to cover the assessment of new drugs by translating useful articles published by other ISDB members. We also publish pieces to raise awareness of the lack of information about paediatric dosages and formulations, items about advocacy in rational use of medicines, articles on antimicrobial resistance, and pharmacoeconomic analyses of different groups of medicines especially those used in the treatment of tuberculosis and AIDS.

What is your main challenge for the future?

The main challenge for MEDEX is competition with the National Drug Bulletin that is published by the National Drug Agency of Moldova with financial support from pharmaceutical companies and indirect but honourable support of WHO–Euro.

RDU Update, Philippines: A Conversation

Isidro Sia

Why was your bulletin started and how long has it been going?

In the early 1990s, a collaborative Philippine–Australia project took place to develop a National Drug Policy for the Philippines. As a result, the Philippine National Drug Information Center (NDIC) was established at the Department of Pharmacology and Toxicology, College of Medicine, University of the Philippines.

The objectives of the NDIC cover aspects of service, training and research. These are:

1. To collect, collate, and evaluate information relating to drugs,
2. To provide and disseminate objective, unbiased and up-to-date information to healthcare providers, policy makers and consumers (i.e. publication of RDU Update),
3. To conduct training and research on matters related to drug information, and
4. To advocate and promote rational drug use.

The first edition of RDU Update was published in 1993.

How often do you publish it and who receives it?

The bulletin is published quarterly. The primary target audience is the 1494 municipal health stations of the country, which are mainly responsible for the selection, procurement and distribution of medicines in their respective areas. The reach of RDU Update is limited because of financial constraints.

What resources do you have to produce the bulletin?

RDU Update is published by the NDIC, which receives support from the Foundation for the National Drug Information Center, a non-government organisation advocating rational use of medicines in the Philippines.

The NDIC currently has two full-time staff, six volunteers and *pro bono* consultants from academia, non-government organisations and health professionals. Part of the work of the NDIC staff is the publication of the RDU Update.

What kind of issues do you cover in your bulletin?

The bulletin features articles that address the practical concerns encountered by Filipino physicians in their daily practice. The Filipino people are heavy users of a variety of health supplements with unsubstantiated benefits and there are many questions surrounding the use of these substances. So, an important role for RDU Update is to publish objective assessments of these supplements.

The NDIC receives inquiries from the public and healthcare providers by email, telephone and SMS. The most common inquiries regard drug interactions, poisoning and the use of health supplements and traditional medicines. To complement the information given to the medical readers of the RDU Update, the NDIC also publishes educational material for community health workers and the public.

Do you liaise with other like-minded organisations in your area?

The NDIC provides drug information services, training, research, networking and advocacy to its ever growing audience base; consistently espousing the promotion of rational drug use in the Philippines.

To realise its mandate, NDIC has forged ties with various regulatory and policy making agencies as well as institutions such as the Philippine Food and Drug Administration, National Center for Pharmaceutical Access and Management, National Adverse Drug Reactions Advisory Committee, and the National Poison Control and Information Service of the Philippine General Hospital.

As part of its networking and advocacy role, the NDIC works in partnership with consumer organisations, NGOs, local government units, academic institutions and international groups in attaining its goals.

The people in the photo are (left to right) Anne Quitain, Leah Dando, Isidro Sia, Cristina Edono, Rainier Galang and AJ Ramos

Not in the photo are Anna Bernardo, Rose Gamoso

ISDB at Work

ISDB committee meetings

The ISDB committee has had two teleconferences in the past six months. One was held in October 2012 and the other in March 2013.

Because the members of the committee live in several different time zones it is not possible to find a time that is convenient for all members. So meeting times have been varied to allow all members to have at least one opportunity to participate in a teleconference. Minutes of the teleconferences are available to members in the members section of the ISDB website.

A face-to-face meeting of the committee will be held in Paris in June 2013. This will be extremely useful because there are some key issues that need to be discussed in a face-to-face situation before they can be resolved.

Transfer of ISDB website

Ciprian Jauca, Therapeutics Initiative

At the end of 2012, the responsibility for the management and maintenance of the ISDB website was transferred to Therapeutics Initiative. Work since then has been mainly focussed on updating the content of the website with current information such as committee members, latest issues of the ISDB newsletter, listing of INFOMED selected citations, etc. The next step will be a review and upgrade of the ISDB Forum feature of the website.

The ISDB Executive Committee will consider the option of calling for proposals for the redesign of the ISDB website later this year. If anyone has any questions or suggestions regarding the website these would be most welcome, so please direct these to Chris Adlparvar (chrisae@ti.ubc.ca)

ISDB Working Group: Communication Using New Technologies

Ciprian Jauca

At the ISDB General Assembly in March 2012, the Working Group on Communication Using New Technologies was established. Apart from myself as coordinator, the only other member of the group is Chris Adlparvar, also from Therapeutics Initiative.

We are in the process of distributing an online survey to find out more about the current practices of ISDB members regarding their use of new technologies and their perceived needs for the near future.

Chris and I would like to welcome some new members to the Group so if you are interested please contact me (jauca@ti.ubc.ca) or Chris (chrisae@ti.ubc.ca).

ISDB General Assembly

The Drug Industry's Invisible Influence on Prescribers: Key Opinion Leaders and Publication Planning

Andrea Tarr

Two of the speakers at the ISDB symposium in Vancouver—Sergio Sismondo (Professor of Philosophy, Queen's University, Kingston, Ontario) and Adriane Fugh-Berman (Georgetown University Medical Center, Pharmacology and Physiology, Washington, DC)—highlighted techniques in knowledge management used by the drug industry to promote their products.

In the pharmaceutical industry, knowledge is a resource to be accumulated, shaped and deployed to best promotional effect. To this end, the industry produces an abundance of special-purpose knowledge, flooding the markets it is most interested in, and distributing it via its most effective channels. This activity includes managing the production of published articles (ghost management) and using third parties, including influential physicians (known as key opinion leaders) to convey marketing messages.

Ghost management of articles is the process by which companies and their agents produce and release articles in medical journals and posters at meetings to establish key marketing messages. They do this by controlling or shaping multiple steps in the research, analysis, writing and publication of articles. Articles are parts of 'publication plans', which treat knowledge as a resource to be efficiently developed, managed and deployed. Specialist publication planning companies exist to do this. In a ghost-written article, a key opinion leader will lend their name to the publication but will have had little role in writing it.[1] The purpose of ghost writing is to: publish key messages according to the marketing timeline, position a product as superior, support off-label marketing campaigns, miminise perception of adverse effects, create doubts about studies adverse to marketing goals and denigrate competitors. Published opinion pieces are vital for

marketing because they provide clear clinical direction, need not be evidence-based and can be used to promote unproven uses of a drug, or to denigrate competing therapies. Specific messages are often embedded in ghost-written articles. Reviews, which summarise research studies and often translate these into clinically relevant recommendations, are particularly important for promoting unproven or disproven uses. For example, efforts to promote menopausal hormone therapy aimed to increase physician awareness on the multitude of benefits that hormone replacement therapy provides for postmenopausal patients and 'diminish the negative perceptions associated with oestrogens and cancer'.[2, 3]

Developing and managing key opinion leaders is a sophisticated activity, with agencies specialised in developing and handling them. There are two categories of key opinion leaders: local and researcher. They are influential doctors who are seen by pharmaceutical companies as sales people. The process of transforming a doctor into a speaker for the company's drugs can take years. Local key opinion leaders are important for giving talks to local doctors while researcher key opinion leaders are paid to speak at conferences, to smooth the path to regulatory approval for medicines and to author ghost-managed medical papers. Key opinion leaders are important for: increasing awareness of invented conditions, expanding diagnostic categories, promoting unproven uses of drugs, changing perceptions about adverse effects or lack of efficacy and battling competing therapies.

Researcher key opinion leaders can be created through advisory boards through which they are asked to give the company advice on the disease or drug or on marketing issues. However, they probably also serve to pass opinion in the other direction, from company to the medical community.

1. Sismondo, S. Ghost management: how much of the medical literature is shaped behind the scenes by the pharmaceutical industry? PLoS Med 2007 4(9): e286. doi:10.1371/journal.pmed.0040286.
2. Fugh-Berman A, McDonald CP, Bell AM, Bethards EC, Scialli AR. Promotional tone in reviews of menopausal hormone therapy after the Women's Health Initiative: an analysis of published articles. PLOS Med 2011; 8(3). http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000425.
3. Fugh-Berman AJ. The haunting of medical journals: how ghostwriting sold "HRT". PLoS Med 2010; 7(9). e1000335. http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000335.

Independence Forum

Sue Phillips and Susan Daskalakis
Therapeutic Guidelines Limited

In October 2012, Therapeutic Guidelines Limited (TGL) hosted an Independence Forum to debate publicly the problem of independence and conflicts of interest in therapeutic information for health professionals. Key objectives were to discuss these issues in the context of the development of therapeutic guidelines for health professionals.

One hundred international and Australian experts from a wide spectrum of medical, research, health policy, ethics and clinical backgrounds attended the forum, see picture at right. Issues discussed included:

- Suitability of clinical research funding
- Limitations of conventional clinical trials
- Reliability of the evidence base
- Competing interests of guideline developers and other experts involved in guideline development.

Two eminent speakers, Professor Silvio Garattini and Assistant Professor Barbara Mintzes, gave an international perspective on the global problem of therapeutic independence. Distinguished Australian clinicians with expertise in bioethics, Professor Paul Komesaroff and Associate Professor Ian Kerridge, facilitated the forum and provided thought-provoking addresses.

Professor Garattini, founder of the Mario Negri Institute for Pharmacological Research in Italy, outlined key regulatory changes that would ensure that only drugs offering true innovation reach the market. These included modifications to the evaluation criteria for new drugs (eg a requirement to demonstrate 'added value') and improved access to clinical trial data. In addition, he stressed the need for improved funding and infrastructure for investigator-driven clinical research, such as the establishment by the Italian government of a fund for independent research using a 5% tax on all pharmaceutical companies' promotional expenses.

Assistant Professor Mintzes, from the University of British Columbia, described the influence of industry funding on the research agenda and the ways in which this can introduce bias—in the design and reporting of clinical trials, and selective reporting of trial results. She suggested key areas for policy change to address the limitations of current clinical evidence, including greater emphasis on priority setting for clinical research; managing industry sponsorship of clinical trials; and the publication, reporting and dissemination of all trial results.

Professor Komesaroff, from Monash University in Melbourne, proposed that interpretations and clinical judgments are not objective and pure representations of the facts; rather, they are subject to the influences of culture and ideology, personal beliefs and reputation, the vested interests of the pharmaceutical industry and medical practitioners, prevailing social prejudices, and politics and power. He stressed that people working to improve clinical practice must recognise these complexities and acknowledge that responsible decision-making always involves the establishment of a careful balance between truth, facts, values and interests.

From left to right: Professor Silvio Garattini, Assistant Professor Barbara Mintzes, Associate Professor Ian Kerridge, TGL Chairman Mr Richard Kneebone, TGL CEO Dr Sue Phillips, Professor Paul Komesaroff, and TGL Consultant (and previous CEO) Mrs Mary Hemming.

Associate Professor Kerridge, from the University of Sydney, spoke about the complex issues of identifying and managing competing interests. He concluded that while disclosure and transparency are important, they are not enough to expunge the possibility of bias. He advocated for the establishment of rigorous, transparent and professionally accepted processes for discussing, assessing and managing competing interests. He called for a more sophisticated view of competing interests and the removal of blame or ignominy from declarations.

During the presentations and discussions many ideas and strategies to reduce the impact of bias and competing interests in guidelines and drug bulletins were proposed. These included ensuring that 'interests' are openly and routinely discussed and managed at guideline development group meetings, and the implementation of rigorous, transparent and professionally accepted processes for discussing, assessing and managing conflicts of interest. Such strategies can help guideline users understand how the independence and integrity of the guideline was safeguarded. TGL is producing a published summary of the Independence Forum proceedings which will soon be available from the TGL website, along with copies of the keynote speakers' presentations.

Publicly Funded Propaganda for Patients

EUPATI Provides Patient Education in the Interest of Manufacturers

Jörg Schaaber

The European Patients' Academy on Therapeutic Innovation (EUPATI) aims to educate patients about new medicines. The influence of the industry on EUPATI has been discussed in an article published by PharmaBrief in Germany. Here is an edited version of a translation of that article, which was originally published in June 2012.

A new initiative plans to educate patients in some key European markets about new pharmaceuticals. However, closer inspection reveals that the pharmaceutical industry has quite a lot of influence within EUPATI.

At first glance the pharmaceutical industry is only one player in EUPATI. Nevertheless, the goals of this 'patients' academy' are tailor-made for commercial purposes. Its scope is limited to new drugs, which can generate large profits for the pharmaceutical industry.[1]

Many of the topics EUPATI would like to draw patients' attention to might as well have come directly from the pharmaceutical industry. EUPATI says 'Pharmaceutical medicines development is a highly regulated, costly, long and complex process that is largely unknown to the lay public.'[1] (As if the industry was not already spreading heavily exaggerated figures on the cost of research.[2])

At the launch of EUPATI it was said that 'Educating the public can reduce scrutiny against clinical research and therapeutic innovation'.[1] Presumably this scrutiny includes the sobering assessments of many new pharmaceuticals by independent organisations such as the German Institute for Quality and Efficiency in Health Care (IQWiG) or the English National Institutes for Health and Clinical Excellence (NICE).

New pharma representatives?

EUPATI will train 'expert advocates' on therapeutic innovation. This is an apparent effort to create a new profession—the lay pharma representative. 'With appropriate training, patient advocates can become accepted partners in scientific, ethical and regulatory committees which can accelerate and improve clinical trials, drug development and access strategies.'[1]

This sounds very much like an attempt to influence the benefit—harm assessments of new pharmaceuticals by independent bodies which are becoming ever more important in many countries – Germany included. It also sounds like a way of increasing pressure to approve new drugs even more rapidly.

Who is behind EUPATI?

The EUPATI logo looks quite official, as if it were an initiative of the European Union (EU), but EUPATI is not an EU project. It is not easy to find out exactly who is behind EUPATI. Three of the four participating patient organisations are mainly funded by industry.

The project is led by the European Patients' Forum (EPF), which receives over 80% of its funding from industry (almost €500 000 in 2010).[3] Another patient association involved, is the International Alliance of Patients Organisations (IAPO), which EPF describes as its 'sister organisation at global level'.[4] The pharmaceutical industry also helped to establish this organisation in 1999.[5] At the time, a board member emphasised that the 'IAPO has a very strong partnership with the pharmaceutical industry'.[6] IAPO is still dependent on industry as only 2% of its budget is covered by membership fees.[7]

Industry plays a key role

The impression of the industry's influence is confirmed by taking a closer look at EUPATI's financing. Almost half of its funds come directly from the European Federation of Pharmaceutical Industries and Associations (EFPIA) and are 'in kind' rather than in cash. This raises the fear that all of EUPATI's activities are being conducted with overwhelming involvement of company employees. The German Association of Research-Based Pharmaceutical Companies (vfa) is also active as a part of the EUPATI consortium and is seeking support from German patient associations.

EUPATI says that 'The Consortium has been structured to optimise synergies with the EFPIA companies to galvanise the most effective, transparent and credible partnership possible and harness the companies' expertise … EFPIA partners not only provide genuine expertise in medicines research and development, but also on their experience in providing information to patients'.[8]

Who is paying?

EUPATI has funding of €10.1 million from the Innovative Medicines Initiative (IMI) for five years. IMI is a public-private partnership between the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Commission. It is supposed to promote pharmaceutical research in areas that the industry considers necessary, but which are not profitable.[9]

IMI could be regarded as a successful move by the pharmaceutical industry to push costs onto the community especially because the Commission is funding IMI with a total of €1 billion over several years, but the pharmaceutical companies are providing their share 'in kind', not in cash. Funding EUPATI as part of this program can at best be attributed to it being one aspect of the 'patients' academy'—recruiting participants for pharmaceutical trials.

Advisory boards

EUPATI has advisory boards[10] but they could be being used as a cloak of independence. Some independent experts have joined its panel of experts. Because of their participation, some patient advocates, who are sceptical of the industry involvement in EUPATI, are considering collaborating. However, it is doubtful whether these experts can ensure that EUPATI will produce only complete and balanced information. Their job is to advise – others will be carrying out the program.

These expert advisors are truly considered to be an external critical force, because EUPATI plans to document their recommendations and record which of them have been followed.[10] A similar level of transparency concerning the industry's involvement in EUPATI would be desirable.

There is growing international consensus that continuing medical education should be kept free of industry influence in order to prevent irrational prescriptions. The exact opposite is now happening with EUPATI. Patients are far less able to guard themselves against the suggestions of the pharmaceutical industry. The independent experts risk giving credibility to the industry's influence on continuing medical education. At the start of 2013, one of the invited expert groups, the IQWiG withdrew from the panel. It said 'We realised that we could not influence the basic conditions under which the project is run. The work had already been started before a consolidated opinion of the expert panel had been agreed upon.'[11]

Leaving the fox to guard the henhouse

It is certainly a good idea for both healthy and ill people to learn more about pharmaceuticals. However, EUPATI can hardly be expected to provide unbiased information. That possibility is ruled out by EUPATI restricting its activities to 'pharmaceutical innovations'. How is it possible to arrive at a neutral assessment when conventional effective treatments are excluded?

Independent health information is important for both lay people and experts. The public sector must take responsibility and serve public safety as well as preventing unnecessary funding of 'pseudo-innovation'.

1. www.patientsacademy.eu/index.php/en/news/2-eupati-launch [accessed 6 Aug 2012]
2. Pharma-Brief (2011) Was Forschung wirklich kostet. Nr. 2-3, S. 3
3. www.eu-patient.eu/About-EPF/Economy/Support/Support-2010/ [Accessed 13 June 2012]
4. www.eu-patient.eu/About-EPF/Responses/EPF-responded-to-the-Commissionsconsultation-of-financial-regulation-to-ensurecore-funding-for-patient-groups/ [Accessed 13 June 2012]
5. www.patientsorganizations.org/showarticle.pl?id=783&n=1251 [Accessed 12 June 2012]
6. HAI News (1999) No. 7 www.haiweb.org/pubs/hainews/June1999.html
7. IAPO (2011) Financial Report 2010 www.patientsorganizations.org/attach.pl/19/1142/IAPO%20Annual%20Financial%20Report%202010.pdf [Accessed 6 Aug 2012]
8. www.patientsacademy.eu/index.php/en/about-Eupati/9-the-consortium [Accessed 13 June 2012]
9. www.imi.europa.eu/content/mission [Accessed 12 June 2012]
10. www.patientsacademy.eu/index.php/en/about-Eupati/15-advisors [Accessed 13 June 2012]
11. IQWiG (2013) Personal communication to Pharma-Brief 12 March

European Medicines Agency Access to Clinical Trials Data Advisory Groups

Prepared by John Dowden based on information provided by participants, including Teresa Alves, Juan Erviti, Andrew Herxheimer, Javier Garjón, Gisela Schott and Florence Vandevelde

The European Medicines Agency (EMA) is responsible for evaluating applications to market medicines in the European Union. Its decisions on approving medicines are based on clinical trial data. Since 2010, the EMA has been releasing some of these data on request. It is now working towards proactively publishing all the trial data it has assessed.

Before proactive publication can begin there are practical and legal implications that need to be resolved. The EMA has therefore organised open discussions on the principles and components that need to be considered. It has established five advisory groups to enable dialogue with stakeholders including ISDB. These groups are named by the topics they are discussing. These are:

1. Protecting patient confidentiality
2. Clinical trials data format
3. Rules of engagement
4. Good analysis practices
5. Legal aspects

ISDB members and other independent organisations, such as the Cochrane Collaboration and Health Action International are participating in each group and are able to share their views on the importance of releasing clinical data. The meetings have been organised as virtual meetings using Adobe Connect, an Internet conferencing system.

The initial discussions took place from the end of January to early February 2013. More meetings will follow. It is expected that the final advice from the advisory groups will be delivered by 30 April and that the EMA will release a draft policy for consultation between 30 June and 30 September 2013. The EMA plans to publish its final policy by the end of November 2013. The policy should come into effect on 1 January 2014.

The EMA has now sent all participants in groups 1 to 4 a summary of their first discussion with the conclusions so far and invited comments. Reports from ISDB members about what has been happening in their groups are described below.

Protecting patient confidentiality

This group has 56 members, including 12 academics, 16 people from industry, seven from patients' organisations and three from non-government organisations. The EMA circulated an introduction with the proposed agenda, participants were offered a practice

session with Adobe Connect beforehand, and could email comments for discussion at the first meeting on 5 February 2013. Andrew Herxheimer sent one observation:

"The proposal assumes that only the EMA and the trial sponsor have the responsibility for protecting patient confidentiality. In my view the overriding ethical responsibility should rest with the lead investigator of the trial, though the EMA and the sponsor must support him or her in fulfilling this responsibility.

This argument derives from the experience of the last 50 years, in which adverse effects of medicines have been universally underreported and inadequately investigated, partly because patients have not been systematically followed up. Most are systematically lost to follow up, largely or partly because confidentiality rules have made it very difficult. The early detection and investigation of harmful effects is in the interests of patients and the community, and if patients understand that they will accept it and work together with professionals.

When invited to take part in a trial all patients should be asked to agree to being followed up by the trial team or its successors (but not the trial sponsor or a body acting on its behalf). Follow up should be a separate part of the trial plan, for which the lead investigator should be responsible. The investigator would therefore be the custodian of the patients' personal data, and so equipped to investigate later harms."

A logical consequence noted in discussion would be that people who did not agree to follow-up when necessary could not be included in a trial.

Clinical trials data format

There are over 60 participants in this group, most of them working for drug companies. They are discussing how clinical trial information needs to be provided in a format that can be analysed, but does not place a burden on stakeholders, such as drug companies.

The first meeting was on 4 February 2013. It was agreed that there is a need to define formats for publishing individual patient data. However, some participants including a representative from the Cochrane Collaboration suggested that this discussion should not be used as an excuse not to release the information. Any format used by regulatory agencies could be acceptable in the meantime.

It was agreed that the formats should ensure privacy protection. Three levels of clinical data and corresponding formats will be included:

- Full clinical study reports: acceptable in PDF format for all approved medicinal products.
- Datasets and results used for the evaluation linked to the relevant protocols; full statistical analysis plan, details on methods and metadata are to always be made available to allow a meaningful re-assessment.
- Individual data such as case report forms in PDF format are neither useful (as they will require substantial manpower for reloading in another usable format) nor appropriate as they may contain patient identifiers breaching privacy protection. Data from the annotated case report forms are to be included in the format.

It was mentioned that more detailed discussion is needed on what additional elements shall be provided along with the datasets. The agreed formats are to be adhered to by all stakeholders and also for locally run trials outside Europe. The applicants should ensure correct implementation of the formats and should also consider the implication of translations from different languages. For trials owned in different measure by different partners (e.g. public—private partnerships), the above points should be taken into account from the beginning of the clinical studies.

The group recommended the policy be implemented from January 2014.

Rules of engagement

This group is discussing what rules (if any) should be in place for external people to be able to access clinical trial data held by the EMA. Pharmaceutical companies have requested that the industry should be consulted before any disclosure, while others underline that public disclosure should be the rule given the overriding public interest.

The group has several questions to consider:

- Should people have to identify themselves to access:
  - aggregate data?
  - patient-level data?
- Should people requesting data be required to agree to respect personal data protection?
- Should people requesting data be required to agree not to use the information for commercial purposes?
- Should people requesting data be made aware of the quality standards for secondary analyses?
- Should people requesting data have to declare if they have a protocol for analysis of the information?
- Should people be allowed to share the data they have accessed?
- Should people who re-analyse the data, feedback their results to EMA?
- How should EMA's policy to make data available be implemented?

So far there has been limited agreement on how to respond to these questions. There will be further discussions at a future meeting.

Good analysis practice

There are about 40 members of this group from different organisations and companies.

At the virtual meeting on 29 January 2013, the most important point Hans-Georg Eichler, medical director of the EMA, made was that the EMA will not be able to make any conditions, if researchers ask for raw study data. There will be no central review and approval of a study protocol as a prerequisite for data release. It will be up to the researchers to follow the recommendations of the EMA, some of which were discussed by the group.

There was general agreement that a formal protocol is desirable in order to facilitate the interpretation of the research and provide some defence against erroneous conclusions related to multiple analyses. The problem that a researcher needs to know the dataset to write a protocol was addressed. Most of the participants thought that protocols should be publically accessible. However, some strong reservations were expressed based on the potential use of litigation by companies to prevent legitimate research.

It was suggested that the same rules should be applied to providers of data (pharmaceutical companies) who should make their analysis protocols public. Open access to computer codes used for analysis and to interim datasets would further promote transparency.

An attempt to make the involvement of statisticians of the pharmaceutical companies obligatory was rejected.

In terms of guidelines for analysis, the general opinion was that EMA should note that researchers should be expected to be aware of relevant guidelines and apply them. Examples include the ENCePP Code of Conduct and Guide on Methodological Standards in Pharmacoepidemiology and the CONSORT statement for reporting research.

Legal aspects

This group is considering issues such as when data can be considered to be commercial-in-confidence.

After the first meeting, there was an impression that the group was dominated by the pharmaceutical industry. Sharing information is in the public interest, but the industry has a view that it owns the data from clinical trials.

The data come from patients. These patients expect that their participation in a trial will advance science. It is therefore an ethical principle that this information should be available as a public good.

It is important for public health that information is not hidden. Transparency enables people to assess the reliability of the data and reduces the chance of research being unnecessarily repeated. This should help to reduce publication bias resulting from the selective publication of positive studies. Transparency also allows people to assess the activity of the EMA.

Our view is that any exceptions to freedom of information should require a detailed substantiation by the drug company that there would be an 'unreasonable degree of prejudice to the commercial interests if the information would be disclosed' based on objective elements for justification. This should be done at the time when the sponsor provides the data to the EMA. It should never apply to an entire document (only the commercial parts or figures can be blacked out). It should only be granted on a temporary basis: the period of time for which commercial confidentiality is required has to be duly specified and notified to the requesting person.

It should be up to the EMA to decide whether or not it agrees with the proposal to classify some parts of documents as 'commercially confidential', taking into account that an overriding public interest justifies immediate disclosure. The proposal made by the European Federation of Pharmaceutical Industries and Associations (EFPIA) to act as a censor deciding whether or not to allow the EMA to disclose the requested documents is unacceptable.

While the industry may have concerns about releasing information that may affect its business, the industry already receives rewards for producing the data. For example, if the data from clinical trials result in a successful application to market a new drug, the industry will benefit from patent protection. Sharing data may encourage greater competiveness in the industry.

Cochrane Under Influence

Assessment of the HPV-Vaccines and Conflict of Interest

Jörg Schaaber

Cochrane Collaboration reviews of therapeutic interventions in medicine are an important source of information for drug bulletins and prescribers. However, there is growing concern that the pharmaceutical industry is trying to hijack Cochrane reviews for its own purposes. The ongoing review of the HPV-vaccines[1] exemplifies this.

Systematic review of evidence about a treatment is fundamental to rational therapy. The Cochrane Collaboration is an important actor in this field. In 2003, industry influence on Cochrane had already led to heated debates[2] and the introduction of some safeguards in 2006.[3] But the rules are obviously inadequate.

The protocol for the Cochrane review of the HPV-vaccines[1] includes a vast array of conflicts of interest. Of the 12 authors who have a major role in the review, two-thirds (eight) have a conflict of interest with both vaccine manufacturers, and two of them were involved in key studies of the vaccine.

One of them, J Dillner, is involved in many steps of the ongoing Cochrane review: designing of the study, giving methodological support and writing the review. He also participates in the final 'critical review' of what he has written by himself,[5] which may perpetuate the misinterpretation of data. In my view, this is very problematic as Dillner was the main author of the publication of the four-year data of the FUTURE I/II studies.[4] In these studies, the presentation of data was selective and misleading and important data were unpublished.[5]

The other Cochrane author involved in the same studies is M Steben. Unlike Dillner, he did not even mention his involvement in the very studies the Cochrane review will assess. When asked by a journalist why he did not mention this he answered: 'As I am working for a public institute I consider myself independent'.[6] Steben also runs his own company. He declared in the Cochrane protocol that he received support from numerous pharmaceutical manufacturers (including both vaccine manufacturers) personally, for his company and the institute that he is working for.

Other authors of the Cochrane review are also worth examination. A Schneider was involved in a trial of one of the vaccines[7] but did not mention it in the Cochrane protocol. A Hildesheim is involved in an ongoing trial[1]

Steben and Schneider have also acted as key opinion leaders for the HPV-vaccination. Steben labelled the HPV-vaccine in the *Canadian Family Physician* as a 'super vaccine'.[8] Schneider claimed in an internet video that the vaccine is 'free of side effects'.[6]

Two other prominent Cochrane researchers reject the common argument that all good researchers have conflicts of interest. Tom Jefferson calls this nonsense. Peter Gøtzsche from the Nordic Cochrane Centre adds that good methodological and statistical knowledge is key for a systematic review but not necessarily close knowledge of the subject.[6]

ISDB has brought these concerns to the attention of the Cochrane Editorial Unit, which has discussed the problems and has passed the issue over to the Cochrane Funding Arbiter Panel.[9] The outcome is not yet known.

1. Arbyn M, Bryant A, Beutels P et al. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors (Protocol). Cochrane Database of Systematic Reviews 2011; 4: CD009069.
2. Moynihan R. Cochrane plans to allay fears over industry influence. BMJ 2003; 327: 1005.1.
3. The Cochrane Collaboration. Commercial sponsorship and The Cochrane Collaboration. 2013; http://www.cochrane.org/about-us/commercial-sponsorship [accessed 17 March 2013].
4. FUTURE I/II Study Group, Dillner J, Kjaer SK et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. BMJ 2010; 341: c3493.
5. Gerhardus A, Razum O. A long story made too short: surrogate variables and the communication of HPV vaccine trial results. J Epidemiol Community Health 2010; 64 (5): 377.
6. Berndt C. Wie sich die Pharmaindustrie in die Forschung einschleicht. Süddeutsche Zeitung 2013; 22 Feb.
7. Schwarz T et al. Persistence of immune response to HPV vaccine. Human Vaccines 2011; 7 (9): 958.
8. Steben M. Do you approve of spending $300 million on HPV vaccination? Can Fam Physician 2008; 54: 174-7.
9. Mail from David Tovey to ISDB 15 Jan. 2013.