

# Medical Writing

Medical Writing in Paediatrics

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### Themes of upcoming issues of *Medical Writing*

The theme of the September issue is 'Writing Matters'. This issue is now closed.

The theme of the December issue is 'Diabetes/obesity' and the deadline is 3<sup>rd</sup> September 2012. All correspondence relating to this issue should be addressed to [editor@emwa.org](mailto:editor@emwa.org) as should letters to the editor, general articles on medical writing and suggestions for future theme topics.

The theme of the March 2013 issue is 'Medical Writing Education'. Articles are requested on the opportunities and resources available, how to become a medical writer, how to teach medical writing, how to teach medical English and where to learn it, how to create a good EMWA workshop, and reviews of textbooks relevant to medical writing or any other topic which prospective authors consider to fall within the Medical Writing Education theme. Correspondence relating to this issue should be address to Phil Leventhal at [phil.leventhal@gmail.com](mailto:phil.leventhal@gmail.com)

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# Medical writing in paediatrics: Children and the future

Elise Langdon-Neuner

Editor, *Medical Writing*

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## Editorial

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'Children are one-third of our population and all of our future.'

*Select Panel for the Promotion of Child Health, 1981*

With the falling birth rate I wonder if they still are a third of the population, but there is no doubt that they are our future. In drug research, however, recognition of the importance of differentiating children from adults has been tardy. Graham Blakey, in his pharmacokinetics series in this issue, explains how pharmacokinetics changes with age and discusses dosing for children. He emphasizes that children are not 'small adults' and cites alarming figures: around 70% of the medicines given to the paediatric population and 93% of the medicines given to critically ill neonates remain unlicensed or are used off-label. It is only now that regulators are forcing researchers to consider children in their own right. Under new EU legislation, the paediatric investigation plan (PIP), research is required to be conducted in children so that in future dosing regimens meet their specific needs.

This issue of *Medical Writing (MEW)* focuses on the recent EU legislation and all its ramifications for medical writers, and reflects the 'paediatrics and vulnerable populations' focus of EMWA's 34th conference, which was held in Cyprus in May this year. The issue gathers together material from some excellent presentations at the conference. EU legislation now requires that an applicant for marketing approval of any drug must have a PIP or a waiver in place. This plan or waiver needs to have been agreed with the European Medicines Agency (EMA). Three articles in this issue concentrate on different aspects of developing drugs for children, and negotiating and preparing applications for a PIP or waiver.

Klaus Rose, a consultant specializing in paediatric drug development, has experienced an increasing involvement of medical writers in designing overall plans in paediatric drug development and negotiating a programme with regulatory bodies. Very much with the medical writer in mind, he

explains the background to the current legislation in Europe as well as that of its equivalent in the USA. He suggests the questions that need to be considered when developing a drug that is intended for use in children and explains the phases of the PIP life cycle. His article also touches on the special aspects of clinical trials in children and what the future holds for paediatric drug development, bearing in mind the high research costs involved.

Paolo Tomasi from the EMA provides guidance in his article on increasing the chances of securing a rapid and positive outcome of the application procedure. Medical writers will find his tips very useful, especially his discussion of applicants' frequent misunderstandings and mistakes.

Douglas Fiebig, an experienced medical writer in the field and EMWA veteran, tackles more specific aspects of writing the PIP application and planning the resources and timelines.

We are also pleased to publish two articles based on important presentations at the EMWA conference that cover more general aspects of medical writing. Mick Foy from the British Medicines and Healthcare products Regulatory Agency (MHRA) reports on the European medicines legislation which aims to improve pharmacovigilance. This legislation will bring about the biggest changes since the current system was created in 1995 and the article provides a starting point for medical writers to get to grips with the new procedures. Again concentrating on the medical writer's perspective, Theo Raynor gives some insight into his research at Leeds University in the United Kingdom on presenting information to patients. He seeks to establish what sort of information patients want and how this information can be written and delivered so as to be accessible and understandable. His investigations cover user testing, readability, and risk communication. An important aspect for the public is 'benefit', where there is still a long way to go in providing information despite specifications that it be included. Theo emphasizes that people need to be able to balance the chance of benefit from taking a

medicine against the risk of harm, but his research suggests that including 'benefit' information in numerical terms may pose problems for the industry because when the benefit is so presented patients think it too low.

Although Theo writes about how to present information to patients, the concept of patients as passive consumers of information is becoming a thing of the past. Ursula Schoenberg's article on crowd sourcing describes a fascinating revolution in which patients are not only discussing health problems and creating support groups on the web, but are also initiating their own studies.

The importance of the web for medical writers and their businesses has not been forgotten either in this issue of *MEW*. Bilal Bham has written a dummies' guide for medical writers who have not yet exploited the possibilities offered by networking websites like LinkedIn and Twitter®. And after you have mastered this you might like to progress to promoting your business with an online video presentation. All you will need is a camcorder and a laptop, as Phil Moran explains in his article on the moving image and your business.

Indeed, EMWA has its own example of video promotion. In a short video on EMWA's homepage ([www.emwa.org](http://www.emwa.org)) Helen Baldwin, an EMWA

past-president, talks about medical writing as a career and about the Association in general. Adam Jacobs, another EMWA past-president, has put together a podcast, which reveals the variety of careers open to medical writers (see box, below).

Returning to the 'children' theme, Melanie Price and Diana Raffelsbauer discuss what must be the most controversial disorder to emerge in childhood, attention deficit/hyperactivity disorder (ADHD). Questions of cause and possible treatment which were not raised when children such as Fidgety Phil in Heinrich Hoffman's book '*Struwwelpeter*' (Shock-headed Peter) were chided for being naughty are now asked under the auspices of ADHD. But is ADHD a true neurodevelopmental disorder? The reviewer of this article who runs a society for ADHD sufferers and their relatives applauded Melanie and Diana's comprehensive and fair discussion of the current literature.

Children are our future, and among the children of today are the scientists of tomorrow. It is therefore fitting that we publish an article from a promising young scientist in this issue. Cameron Hamilton won a well-deserved prize for his essay entitled 'Are stem cells the future of healthcare?' The informative and clear style of the article is certainly on my wish list for the future of science writing.

## Medical writers' work: Podcast from EMWA conference

At the EMWA conference in Cyprus, I kept a little audio diary of the conference, in which I talked to various medical writers about their work. No two medical writers I talked to had the same job, showing what a beautifully varied profession medical writing is. If you'd like to listen to the diary as a podcast, you can download it at <http://dianthus.co.uk/emwa-conference-podcast>. The full version lasts about 48 minutes, but if you're short of time, there's also an edited version which lasts just under 10 minutes.

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# Message from the President

Susan Bhatti

*EMWA President*

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## Dear Members

I am sure you are all very familiar with this situation – sitting in front of a blank piece of paper (or to be more accurate a blank screen) and wondering where to start. Beginnings and endings always seem to be the trickiest part, but I have opted for the classical medical writing approach, and will start with an introduction.

I joined EMWA when the organisation was still in its infancy, and was indeed only a small ‘chapter’ of the American Medical Writers Association. I can still vividly remember the first conference I attended in Edinburgh in 1997 and how impressed I was with the friendliness of all the medical writers I met there and the sheer fun of the whole event. I returned from that conference, decided to join the association, and have been an EMWA member ever since. After that initial step it was not long before I had volunteered to be a workshop leader and then eventually last year I threw caution to the winds and stepped up to join the Executive Committee as Vice President. And now here I am writing to you all knowing that when you read this there will be several new members on the EC, the spring conference in Cyprus will already be over, and the plans for the autumn conference in Berlin will be in full swing with a long list of ‘to dos’ on the agenda.

So what are the plans for EMWA as the organisation enters its twenty-first year? Well we are a thriving and growing organisation, and while not unexpectedly most of our membership is still based in Europe, most of these are from North Western Europe. So one of the top priorities is to try to expand the membership base into countries where we are currently underrepresented. And although we are obviously a European association, many of us work in global organisations so we also want to reach out beyond the borders and look for ways to cooperate with scientific writing associations in other parts of the world. Initiatives have already been started in this direction with the Institute of Clinical Research (ICR) and the International Society for Medical Publication Professionals (ISMPP) and others are to follow. By

becoming more international and creating networks with other organisations, the value of being an EMWA member will increase and the association will be able to have more impact on the medical writing profession worldwide.

A further field for development is to increase our use of electronic media. Although we all email, Skype and Google, I realise that as an organisation we still tend to be rather old fashioned when it comes to communication. However, if we want to reach out beyond our current boundaries and attract the next generation of medical writers to join EMWA, it is essential that we do not miss the opportunities that the WWW provides in order to enhance our reputation. Indeed to start this ball rolling, this is the first message from the president that you will all receive by email and not just be able to read in the journal. Any suggestions by members on how we can improve and increase the dialogue with medical writers around the world are very welcome, so please let us have your ideas!

Of course the EMWA conferences and the EMWA professional development programme (EPDP) will still continue to provide a foundation for the organisation. Happily the attendance at these conferences is still excellent and we are obviously offering a valuable learning programme to people working in the medical writing profession. However, I do realise that only a small proportion of our members are able to attend the conferences and so we will be looking into ways in which we can enable more EMWA members to benefit from the extensive experience within the association. Although it is not a substitute for face-to-face learning, I am aware that there is an increasing demand for interactive online seminars, and this would certainly help our members who are located outside Europe to link up with EMWA. Again any ideas and feedback from members on this topic is more than welcome!

While writing this message I have been browsing through the past issues of our journal on the website and realised that similar topics to the above have featured on the agenda of previous EMWA presidents. So while it is easy to make plans, the real

challenge is to implement them and bring about significant changes. A year passes very quickly and just coping with the day-to-day work of running an organisation tends to use up much of the available 'spare' time of the EC members outside of their full time jobs. But I will remain optimistic and can promise all of you that I will work with the committee to ensure that EMWA continues to offer a professional learning and communication platform to medical writers, which meets their needs while retaining what I feel is the most essential part – namely the spirit of true sharing of experience and lasting friendship.

So here I am at the end of my first president's message and stuck with the problem of how to finish on an upbeat note that speaks to the heart and doubles the membership numbers overnight. Fortunately, the late Geoff Hall (a founder member of EMWA and a true friend) already put it in a nutshell in an article he wrote for the journal in 2008, 'for me the main benefit of EMWA membership has been the friendships made. It seems somehow bizarre that several of the people I consider among my closest friends are people who I only see for a few days each year'. I can only echo his words.

June 2012

**35th EMWA Conference  
8–10 November 2012  
Andels Hotel  
Berlin, Germany**

We are delighted to announce that the venue for EMWA's 35th conference will be the Anders hotel ([www.andelsberlin.com](http://www.andelsberlin.com)) which is situated in the east of Berlin. The hotel claims to be a must for lovers of architecture and design and as anybody who attended the last EMWA conference in Berlin will know the city has an exceptional flare and many interesting sights.

We will be offering an extensive range of workshops on medical writing topics for those wishing to secure credits towards their foundation or

advanced EMWA professional development programme certificates or to keep up to date with emerging knowledge in the field. It will also, as always, be a great opportunity for networking and meeting up with colleagues and friends.

For further details see the EMWA website at [www.emwa.org](http://www.emwa.org)

The 36th EMWA Conference will be at the Manchester Central Convention Complex, Manchester, United Kingdom from 7th to 11th May 2013.

# Challenges of paediatric drug development and impact of paediatric legislation

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## Abstract

Medical writers are increasingly involved in designing and documenting overall plans in paediatric drug development, e.g. EU PIPs (Paediatric Investigation Plans) and individual components, e.g. protocols and study reports. It is essential to differentiate between the overall process and the individual components that together constitute paediatric drug development. Paediatric drug development does not mirror the development of drugs for adults. Drugs are developed by commercial companies. Paediatric drug development was triggered by laws dating back to 1997 (USA) and 2007 (EU) to give children better access to pharmaceutical progress. The active players are the regulatory authorities, the respective company, and the professionals involved in the planning and execution of defined development activities. For companies, participation is partially voluntary in the USA but compulsory in Europe. Key elements are assessing epidemiology and existing therapies in children, and all elements of adult drug development adapted to children's different anatomy, metabolism, and developmental stage. Paediatric drug development might include, for example, developing liquid formulations for children (vs. tablets), doing studies in juvenile animals, and paediatric clinical studies. Most key components of the paediatric drug development plan are negotiated between authority and company, and executed by paediatricians, clinical pharmacologists, and others.

**Keywords:** Paediatric drug development, Paediatric Investigation Plans, Pediatric legislation

## Introduction

With few exceptions, paediatric drug development does not mirror adult drug development. Some companies do develop drugs for children, e.g. vaccine developers or companies targeting rare

paediatric diseases. In general, drug development is market-driven by companies competing in the business world. Paediatric drug development is funded by an industry that develops predominantly adult medicines. In the USA in 1997 the FDAMA (FDA Modernization Act) offered 6 months patent extension in return for voluntary drug research in children. This was complemented in 2003 by the mandatory PREA (Pediatric Research Equity Act).<sup>1</sup> These laws are required to be re-authorized every 5 years, the next re-authorization being due in summer 2012. The EU paediatric regulation, in force since 2007, added new momentum to the development of drugs for children.<sup>2,3</sup> This legislation is intended to ensure that children are considered within the process of development of drugs for adults. This is relatively straightforward where a disease exists both in adults and in children, and is more complex when this is not so, but where a drug might have another use in children, e.g. ibuprofen for persistent arterial duct in newborns. Specifically, targeted paediatric drug development would require a different framework.

## US pediatric legislation and background factors

Fig. 1 is a showcard from 1918 with a drug labelled for adults and children. Fig. 2, from slightly earlier, is for a product advertised for children only. These labels show only limited comparability with today's labels, which describe only the proven properties of the respective medicine. It was different in 1918. Dr Arnold's cough killer contained morphine. It certainly suppressed cough, but it could also kill children. These drugs were on-label, but in these days the label could claim anything. The manufacturer didn't have to prove these claims.

In the USA, it is only since 1962 that drug manufacturers have had to prove the efficacy and safety of their medicines. Only since then have modern drug



Figure 1: Lung tonic for coughs, colds, and chest trouble, suitable for children and adults. Showcard 1918. Source: [www.wellcomecollection.org](http://www.wellcomecollection.org).



Figure 2: Dr Seth Arnold's Cough Killer. Colour trade advertisement, 1800s. Like many nineteenth-century over-the-counter medicines, much of its effect was due to the fact that it contained a narcotic drug or hallucinogen, in this case morphine, a derivative of opium. People were unwittingly being exposed to habit-forming drugs, something the American Medical Association started investigating about this time. It compiled a list of dangerous 'nostrums' in May 1909, including alcohol, opium and its derivatives, morphine and codeine, cocaine, chloral, and cannabis. Legislation followed eventually.

Source: [www.wellcomecollection.org](http://www.wellcomecollection.org).

labels existed. One consequence of the US Kefauver-Harris amendments (1962) was that, to avoid litigation, manufacturers introduced disclaimers that the respective medicine had not been tested in children.<sup>4</sup> Since then much has been learned about children and medicines. Clinical pharmacology has evolved as a science, with paediatric clinical pharmacology as a sub-

specialty,<sup>5,6</sup> adding to our understanding of the maturation of organ systems, children's metabolic pathways, absorption, and excretion.<sup>7</sup> Generations of hospital clinical pharmacologists have spent considerable time procuring hand-made paediatric formulations. Paediatric clinical pharmacology evolved by investigating drugs that were already on the market. The 1997 US legislation encouraged the generation of 'some' paediatric data – at a time when for many drugs no paediatric data were available at all.

## EU paediatric legislation: a new approach

The EU paediatric legislation came into force in 2007.<sup>2,3,8</sup> It parallels the US legislation, but its scope is radically increased. Marketing Authorization Applications (MAAs) for any new drug must be submitted with a Paediatric Investigation Plan (PIP) approved by the EMA Paediatric Committee (PDCO), unless the EMA confirms in writing the applicability of a class waiver. Generics are exempt, orphan drugs are not. The EMA CHMP (Committee for Medicinal Products for Human Use) approves new drugs, but the PDCO can block a submission. EMA will not validate a submission without an approved PIP. The PDCO is composed of 33 members plus another 33 alternates. Each member state is represented by one member and one alternate; additional members represent the CHMP, professional paediatric healthcarers' organizations, and patient organizations. The PDCO decides about PIPs, waivers (no development in children) and deferrals (later execution of studies).

The PIP must cover all age groups as defined by ICH E 11: preterm newborns (<36 weeks gestational age), newborns (0–27 days), infants and toddlers (1–23 months), children (2–11 years), and adolescents (12–17 years).<sup>9</sup> It should be submitted at the end of human pharmacokinetics (PK), interpreted by EMA as the end of phase 1, i.e. before proof of concept. It must include plans for preclinical testing, e.g. juvenile animal studies; formulation(s), e.g. intravenous for preterm newborns, liquids for infants and young children; clinical pharmacology for dosing; and clinical trials.

## Development strategy for drugs for children

Drug developers must do their paediatric homework. Within the framework of EU and US legislation, the essential questions are as follows. Does the targeted disease exist in children? From which age onwards? Are the mechanisms of drug and disease comparable enough between adults and



children to allow extrapolation of efficacy? Which dose should be used at which age? What clinical trials are needed? What special formulation(s) are needed? Are studies in juvenile animals of value? The company team will know the adult disease, but for children additional external expertise will be required. The best approach is to reach tentative conclusions within the company, and then to challenge them with a group of external paediatric specialists face-to-face. The PIP is then written. Usually, the first round of 'paediatric negotiations' is with EMA PDCO and negotiations with the FDA come later. If the company's approach is scientifically sound it will be easier to convince the regulatory authorities. EMA PDCO will also ask for paediatric drug development in rare and very rare diseases.

### PIP or paediatric Plan

The PIP life cycle has three phases: preparation; submission and negotiation; execution and modification(s). The PIP submission begins with a letter of intent 2 months before PIP submission (template on the EMA paediatric website<sup>10</sup>). EMA will communicate the names of three key people: the EMA paediatric coordinator, the PDCO rapporteur, and the PDCO peer reviewer. The 20 EMA paediatric coordinators serve as a procedural and administrative link between the applicant and the PDCO. They also help with teleconferences and give procedural advice.

There is no official PIP template, but the 'EMA/PDCO summary report template with internal guidance text'<sup>11</sup> is used by most applicants. The PIP, application form, clinical study form, and a cover letter must be sent to the EMA coordinator and the PDCO rapporteur and peer reviewer by post or courier and via Eudralink. Once the submission is validated, the entire documentation must be sent as a CD-ROM and via Eudralink to all PDCO members and alternates. References are required as PDF files on the CD-ROM. To meet deadlines, receipt via Eudralink is accepted.

The PIP negotiation procedure consists of two 60-day blocks. The PDCO day 30 discussion is documented by a report. The day 60 discussion results in a list of requested modifications, and a clock stop starts. Once the requests for modification have been considered, a response document should be sent to EMA together with the modified PIP. The PDCO will discuss this at day 90, and issue a new list of requested modifications. Last amendments take place between days 90 and 120. For remaining questions an oral explanation may be requested at day 120. If the PDCO is satisfied with the modified PIP content, it issues a positive opinion. If not, the

applicant can choose between a negative opinion, re-examination, or PIP withdrawal. The applicant can also sue at the European Court of Justice. So far, one company has sued and lost both in the first instance and in the main trial.<sup>12,13</sup>

After the PIP is agreed upon, clinical trials and other measures in children begin according to the committed timelines. This can include requests for modification. In EMA's estimation, the average PIP requires 3–5 modifications.<sup>14</sup>

In the USA, for compliance with PREA, the FDA requires a paediatric assessment at the end of the phase 2 meeting, and a Paediatric Plan (PP) at submission. The PP will be reviewed during the approval procedure. For a reward of 6 months patent prolongation, the company can negotiate a written request to investigate the drug for use in children in another indication.<sup>15</sup>

### Clinical trials in children

In the last century, the prevailing opinion was that it would be unethical to expose children to clinical trials. Today mainstream thinking is that it is unethical and more dangerous to treat children with drugs that have never been properly investigated in children. Nevertheless, a skeptical attitude remains. The parents' position also depends on the seriousness of the disease. Almost all children with cancer participate in clinical trials. Thanks to decades of research the diagnosis of acute lymphatic leukaemia in a child is today no longer a death sentence, although still a horror; 80–90% of children survive thanks to cytostatic and other medications developed for adult cancer treatment decades ago.

Phase 1 studies in healthy children are not allowed. However, children receiving treatment can have experimental drugs as add-ons, allowing PK and pharmacodynamics measurements. Clinical trials in children are always more demanding than those in adults. Children are always part of a family, and the clinical investigator must be aware of this. Parents will often visit together with other children. If the study centre is shabby, the study personnel unfriendly, or the scheduled visits too rigid, the parent will not return.

From a legal point of view, parents have to sign the informed consent. The question of whether this should be one or both parents is a nightmare: the requirements are different in each country. From around school-age onwards, children themselves have to be informed and should, as a symbolic act, also sign an assent.

The physical clinical trials are performed by clinicians. There are now many paediatric research

networks in Europe, partially coordinated by the EMA under the European Network for Paediatric Research (Enpr-EMA).<sup>16</sup>

### Other operational challenges

Paediatric clinical trials must be approved by an ethics committee and must be registered with the authorities. Approval by ethics committees has evolved into a major hurdle because many ethics committee members are not experienced in paediatrics and often lack any knowledge of pediatric legislation. There are many more challenges, such as laboratory issues, how much blood can be taken and how often blood can be taken, and the need for adequately trained study personnel.<sup>17</sup>

### Outlook

Paediatric drug development is expensive. The EU gives a reward of 6 months patent extension through a supplementary protection certificate (SPC) but this comes at the end of patent life, while the additional development costs must be paid earlier. A company that has developed a drug up to proof of concept will not abandon it because it has to submit a PIP. EMA classified melanoma as a juvenile disease in view of the incidence of 1.7/100,000 in 15–19 year olds, quoting US Surveillance, Epidemiology, and End Results (SEER) Carcinoma Statistics.<sup>18</sup> However, of the group cited, two-fifths are adults (18- or 19-year-olds). The number of juvenile melanoma patients is probably half of the cited number. In 2011, two companies got a melanoma PIP approved.<sup>19,20</sup> There will come a point where companies will stop investing in therapeutic areas where PDCO demands turn the potential profitability of future drugs around. A possible example might be epilepsy: one new epilepsy compound ended up with 16 trials or measures in the sub-diseases: paediatric epilepsy syndromes; neonatal seizures; epilepsy with partial onset seizures; idiopathic generalized epilepsy with primary generalized tonic clonic seizures.<sup>21</sup>

The pharmaceutical industry was not proactive during the years preceding the EU regulation. The focus was on requesting more months SPC prolongation. During these years, better solutions could have been found. Today, each company is faced with an established EMA paediatric structure. Even if requests are unbalanced, there is little a company can do. The EU paediatric regulation is due for a first review in 2013 and a second one in 2018.

Both sides are learning and will continue to learn. Companies learn during the PIP procedure, the EMA

adapts and individuals learn. The degree of detail in each PIP will be less in the future, as EMA representatives announced at the DIA/EFGCP/EMA paediatric conference in autumn 2011.<sup>22</sup> This will reduce the workload on both sides. Consideration of children is now an essential part of drug development, and this will not go away. The future will show whether the research-based pharmaceutical industry will find a way to switch to a proactive approach. Let's imagine an independent European institute that would work out binding recommendations for each drug, financed by the pharmaceutical industry, with regulators, industry and clinicians on the board of directors. This would probably cost a fraction of what all companies together invested into the more than 1000 PIPs submitted so far. For the moment, each company must negotiate a programme from which children will benefit and that allows the company to survive. Much of this workload is borne by medical writers.

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# Writing applications for Paediatric Investigation Plans and waivers

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## Abstract

Under EU legislation, a Paediatric Investigation Plan (PIP) and/or a waiver must be agreed in advance with the European Medicines Agency (EMA), for all new medicinal products seeking marketing authorization; the same applies for already authorized products under certain circumstances. In principle, the application needs to be submitted early in the development (before completing basic Phase I studies in adults), which may require an innovative and creative approach to the drafting of the necessary documents. The aim of this article is to provide a guide on already existing and available help and advice, to provide further suggestions and comment, and to illustrate common mistakes; the reader should then be able to increase the chances of a more rapid procedure with a higher probability of a positive outcome of the procedure.

**Keywords:** Paediatric Investigation Plan, Waiver, Deferral, EMA, Application, Guideline

## Introduction

The EU Regulation 1901/2006 (<http://bit.ly/tth2CD>) – the ‘Paediatric Regulation’ – provides a systematic approach to the development of medicinal products intended for use in the paediatric population. This legal framework followed the first US initiative (the Best Pharmaceuticals for Children Act), which has been in place since 1997. Pharmaceutical companies are now required to perform clinical studies in children before being able to apply for marketing authorization of a new medicinal product in the EU (or for a new indication, dosage form or route of administration of an authorized, patented product), unless they have agreed a waiver or a deferral with the Paediatric Committee (PDCO) of the European Medicines Agency (EMA).

## *The Paediatric Investigation Plan*

Companies are required to agree with the PDCO of the EMA on the proposed studies and measures to be undertaken for a new medicinal product; this constitutes the so-called Paediatric Investigational Plan (PIP).

A PIP should provide sufficient data to enable the assessment of the quality, safety, and efficacy in children, and consequently the benefit/risk profile in the paediatric population.

When preparing a PIP, the six core questions to be addressed are the following:

1. Is there a need for the candidate medicinal product in children?
2. If there is a need for paediatric development, what is the condition(s) in which paediatric development should occur, considering the proposed indication(s) in adults?
3. In which age group(s)/paediatric subsets should the development take place?
4. Should there be an adapted formulation and a specific non-clinical package?
5. What clinical measures should the paediatric investigation plan contain?
6. Should any measures in the PIP (mainly clinical trials in children) be deferred or not?

If an agreed PIP becomes no longer feasible, or inappropriate due to new scientific knowledge, applicants can always request one or more modifications to the agreed PIP.

## *Deferrals*

Deferrals are the instrument to avoid a delay in marketing authorization in adults. In many cases (but certainly not always), paediatric studies can or should be performed after studies in adults have confirmed the activity and the safety of the product; a deferral to initiate or complete one or

more studies in children may therefore be requested and agreed by the PDCO.

### *Waivers*

Some conditions do not occur in children, or in some subsets of the paediatric population. Therefore, a waiver from the obligation to do studies can be granted by the PDCO. In addition, waivers may be granted when the medicinal product is expected to be unsafe or ineffective in children (or in subsets), and finally when the product appears to have no significant benefit at all over existing treatments for the same condition. Applicants are expected to thoroughly justify, with supporting evidence, any request for a waiver, whether ‘partial’ (specific subsets of the paediatric population) or ‘total’ (applying to all paediatric subsets in a given condition).

### **Available guidance**

A presentation on the resources available to applicants, when developing a PIP or waiver application, is available on the EMA website (<http://bit.ly/xO1T9y>).

More specifically, the official European Commission (EC) Guideline on the format and content for PIP and waiver applications and for compliance check is published on the European Commission’s website (<http://bit.ly/EC-PIP-guidance>). This is the basic guideline that contains all the necessary information on what a PIP/waiver application needs to contain, and is fundamental reading for anyone preparing an application.

While the EC guideline mainly addresses scientific aspects and the content of applications, the various procedural aspects are contained in the questions-and-answers document published on the EMA website (<http://bit.ly/PIP-Proc-Advice>). This contains a pot-pourri of technical and regulatory issues that have arisen most frequently during interaction with applicants; of particular relevance to the preparation of the PIP application are questions 6, 8, and 9. This guidance is also a must-read, particularly before addressing a question to the EMA, as in most cases it will have been covered already in the published answers.

Any document in the EMA website, including scientific guidelines, can be found with the EMA search engine (<http://bit.ly/wtOCmL>); additionally, specific preselected lists of guidelines of paediatric interest are also present (<http://tinyurl.com/paedguidelines>, <http://tinyurl.com/paedguidelines2>). Among the most recently published ones, the following have particular relevance: the Draft guideline ‘Pharmaceutical

Development of Medicines for Paediatric Use’ (<http://tinyurl.com/draftqualitypaeds>), and ‘Investigation of medicinal products in the term and preterm neonate’, (<http://tinyurl.com/EMANEonates>).

The EMA periodically organizes Expert Groups on topics of relevance for the development of paediatric medicines; presentations and outcomes are published on the website (<http://tinyurl.com/PaedExpGroups>).

EMA Decisions on PIPs and waivers, including modifications, are also published and searchable by condition (<http://tinyurl.com/PIPDecisions>).

### **Points to consider**

#### *Adequate justification is of paramount importance*

It is crucial that every request/proposal (for a PIP, for a deferral, a waiver, a specific study...) be properly justified in the PIP application. The PDCO has negatively viewed several PIP/waiver applications, not because the proposals of the applicant were unacceptable in principle, but because they were not properly justified. This meant that there were not enough elements to assess whether the proposal was acceptable or not.

#### *One PIP or multiple PIPs?*

In some situations, when a product is being developed for more than one condition in adults, and the marketing authorization procedures will be separate, it will be convenient to ask two separate PIPs for the same medicinal product, one per condition. This may allow, again under certain circumstances, an earlier reward. Guidance will be published in the EMA website, within Q2 2012, to clarify these aspects.

#### *Mechanism of action*

It is important to describe, in sufficient detail, the putative mechanism of action of the product. The condition for paediatric development is identified by the PDCO also based on the mechanism of action, starting from the proposed indication (in adults).

#### *Pharmaceutical form(s)/quality aspects*

These are to be provided in the application form (Part A) rather than in the scientific documents (Parts B–E). Again, a sufficient level of detail needs to be provided.

#### *Role of extrapolation*

Most paediatric investigation plans contain at least some form of ‘partial’ extrapolation, in the sense that the scale of the development (number of studies, number of patients, etc.) is different from what is done in adults. This rests on the assumption

of at least some similarity in response between adults and children with the same/analogous disease. However, no matter the degree of extrapolation (in some case, it may be acceptable to completely extrapolate efficacy), applicants should be explicit in the justifications for the amount of extrapolation proposed. The EMA has a working group on extrapolation, and the outcomes will be published on the website, starting in 2012.

#### *Presubmission meetings*

The EMA accepts requests for presubmission meetings from prospective applicants, with a view to improving the quality of the application to be submitted and increase the chances of a smoother validation and a final positive opinion at the PDCO. Details about these meetings are available on the Q&A document on the EMA website (Q&A 26 in <http://tinyurl.com/PIPQ-A>).

### **Frequent mistakes/ misunderstandings**

Some misunderstandings seem to occur with greater frequency, and therefore a brief discussion of them is provided here.

- *Insufficient information provided:* Whether in Part A (application form), or in Parts B-E (scientific document), this is likely to lead to non-validation.
- *Excess information provided:* There is no need to provide a detailed discussion of the disease, as can be found in textbooks, for common disorders.
- *Justification:* As already mentioned, providing sufficient justification is crucial, particularly when requesting a waiver or a deferral. For example, it is not sufficient to simply state that a disorder is rare in children, and therefore studies are not feasible, to obtain a waiver. In such cases, a prevalence analysis should be carried out, supported by available literature evidence, expert opinion etc.
- *Deferral:* A frequent source of confusion. When a deferral is requested for, say, completion of a given study, this just means that marketing authorization (MA) in adults can be sought before completing that particular study in children; it does not exempt the applicant from proposing justified and sufficiently detailed elements about how the study will be. Furthermore, even a deferred study must include a proposed completion date (an 'absolute' date, not relative to the foreseen date of

application for MA), and after that date the study will become due, even if, for whatever reason, the application for MA in adults has been postponed.

- *Pharmaceutical form:* While it is understood that not all quality aspects of the product for paediatric use will be known at the time of the application, the applicant still needs to provide a proposal of what will be developed, with sufficient details to allow the PDCO to express an evaluation of the proposal itself.
- *Non-clinical development:* In this section of the application, an explicit discussion of the possible need of studies in juvenile animals should be included. The Non-Clinical Working Group of the PDCO will assess all relevant PIP proposals, to this aim.
- *Clinical studies:* The opinion, to be adopted by the PDCO, will not contain the full details of each study protocol for the clinical trials, but only the key elements, on which compliance check will be done at a later stage. Often applicants are surprised to receive a 'slim' opinion, lacking many of the elements in the full protocol, and request that they are reintroduced: this is not necessary and actually can be counterproductive, as a modification of an agreed PIP may become necessary to change secondary elements of the protocol.
- *Coverage of all paediatric subsets:* All paediatric subsets must be covered in the applications, either with PIP studies, or with a (partial) waiver. A common mistake is the omission of a small subset (say, from 4 to 6 years of age) from the PIP/waiver. In principle, whenever there is a paediatric need, a waiver is inappropriate, and that paediatric subset must be covered by one or more studies in the PIP. Studies may include extrapolation studies.
- *Methodology:* A single-arm, open label study cannot demonstrate efficacy. At best, it can support a claim of activity (usually on a biomarker or surrogate endpoint). That is not to say that these studies are always unacceptable, but proper justifications need to be provided. Also, a commonly encountered omission is the lack of a power analysis/sample size determination, again without justification. While it is acknowledged that rare conditions will be even rarer in children, and that fully powered, controlled efficacy studies are not always possible in children, this does not necessarily imply that a waiver will be granted under these circumstances: limited data on activity and tolerability/safety in small samples may be

acceptable, in some circumstances and again with proper justification. Other common mistakes include: specifying multiple primary endpoints without the correct methodological approach, too wide delta for non-inferiority studies, mixing too many objectives (Phases I, II, and III in the same study), etc.

## Conclusion

A well-written PIP is central to a rapid validation, and increases the chances of a positive opinion by

the PDCO. Several resources are available in the EMA website, and specifically in the two paediatric sections (Regulatory/Paediatric Medicine and Special Topics/Medicines for children); in addition, draft applications can be discussed for further advice during a presubmission meeting. While in paediatric medicines trials may be small, the evidence still needs to be good: the goals of the paediatric regulation include an increased availability of authorized medicines for children, and to this end, the approval of a suitable paediatric investigation plan is a necessary first step.

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## Author information

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# Preparing the Paediatric Investigation Plan application

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## Abstract

In Europe, sponsors must possess a compliant Paediatric Investigation Plan (PIP) when applying for marketing approval of drugs. The core deliverable is the 'scientific part of the application' structured according to the EMA's PIP guideline. The PIP should summarize relevant background information on the disease and drug, and use this to justify a paediatric development programme that covers the entire paediatric population. Depending on the type of drug and the relevance of the disease to the paediatric population, specific quality, safety, and/or efficacy measures may be proposed for all or part of the population. If measures are considered inappropriate for all or part of the paediatric population, then a waiver may be proposed but must be justified. If the paediatric development programme cannot be completed before submission of the adult application, then a deferral of the paediatric measures may be proposed but again this must be justified. In any case, a detailed timetable has to be provided and adhered to for any all measures being proposed. The main challenges for medical writers when writing a PIP are application of the guidance to the drug and disease in hand, and obtaining the appropriate input from the project team.

**Keywords:** Paediatric Investigation Plan, Waiver, Deferral, Paediatric measure, Application

Since enforcement of the Paediatric Regulation in 2007,<sup>1</sup> sponsors must possess a compliant Paediatric Investigation Plan (PIP) when applying for marketing approval of unauthorized drugs, or when applying for approval of new indications, pharmaceutical forms, or routes of administration for currently authorized drugs. The default situation is that a Marketing Authorization Application (MAA) should now include findings from the

paediatric population. These findings have to be obtained in clinical studies designed and conducted according to measures described in a PIP that was agreed upon beforehand by the European Medicines Agency (EMA)'s Paediatric Committee (PDCO). Because the Paediatric Regulation also stipulates that an MAA should not be delayed due to a paediatric development programme, there are also provisions for deferring or waiving some or all paediatric measures, as described below.

The core deliverable for a PIP application is the 'scientific part of the application', which is a document structured according to the EMA's PIP guideline.<sup>2</sup> A length of 'below 50 pages' is recommended, which sounds brief and can lead sponsors preparing a PIP for the first time to underestimate the time and effort required. With this in mind, and assuming the need for a PIP has been established, there are six main steps involved in preparing a PIP application, as outlined in the sections that follow.

## Consult the guideline and associated resources

The final guideline on the structure and content of a PIP was published in September 2008. At first sight this is not a particularly user-friendly document. For example, it often refers to specific articles of the paediatric regulation that themselves are sometimes challenging to interpret. Fortunately, the EMA's website provides a number of other sources of information that can help in preparing a PIP. Foremost among these are the *Electronic form for paediatric investigation plan application and request for waiver* (a PDF file sometimes referred to as the 'PIP template') and the *EMA/PDCO summary report template with internal guidance text*.

A common misconception is that the PDF file referred to above is a template into which text can be inserted for the entire PIP application. This is not the case. Instead, this is a dynamic PDF file that covers Part A of the PIP application. It addresses administrative aspects such as details of the

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applicant, the drug, the intended indication, etc. However, at the end of the file is a table of contents that provides the recommended high-level structure for the scientific part of the application (i.e. including the ‘scientific part of the application’ in Parts B–F). Confusingly, the suggested structure is not identical to the organization provided in the final PIP guideline, but fortunately the difference lies only in the order in which information is provided.

Thus, based on the table of contents given in the PDF file, applicants can create their own templates in a Word file for writing Parts B–F of the application. The high-level structure suggested by the EMA is shown in Table 1, which in practice will need to be augmented with subsections tailored to the specifics of the application.

The *EMA/PDCO summary report template* is used by EMA reviewers to write their assessment reports, which are then used by the PDCO to review the application. The template is helpful for applicants because it provides recommendations on what reviewers should assess and provide comments on.

Thus, by addressing these issues during authoring of the PIP, the writer can tailor the PIP’s content to the PDCO’s expectations and potentially reduce the number of questions arising during review.

## Plan resources and timelines

As with other regulatory documents, realistic planning of resources and timelines is crucial to the timely success of preparing the PIP. Writing a PIP almost always requires more resources and time than initially estimated. This can be partly due to a lack of experience, and partly because PIPs often need to include substantial amounts of text drafted anew rather than text adapted from existing material. As discussed below, such texts include background information on the paediatric population and the disease at hand (which can be difficult to obtain) and the rationale for the measures that constitute the paediatric development strategy (which typically involves lengthy discussions and multiple revisions).

Table 1: Recommended structure of the PIP according to the 2008 EMA guidance in the ‘Application for Paediatric Investigation Plan/Waiver’ (Version 3.0.0)

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PART B – Overall Development of the Medicinal Product Including Information on the Target Diseases/ Conditions
B.1 Similarities and Differences
B.1.1 Discussion on similarities and differences of the disease/condition between populations (including information on prevalence/incidence)
B.1.2 Pharmacological rationale and explanation (including structure, absorption, PK, pharmacodynamics, metabolism, elimination; mechanism of action; similarities and differences of the safety and efficacy profile)
B.2 Current Methods of Diagnosis, Prevention or Treatment in Paediatric Populations
B.3 Significant Therapeutic Benefit/Fulfilment of Therapeutic Needs
PART C – Applications for Product Specific Waiver(s)
C.1 Overview of the Waiver Request(s)
C.2 Grounds for a Product Specific Waiver
C.2.1 Grounds based on lack of efficacy or safety
C.2.2 Grounds based on the disease or condition not occurring in the specified paediatric subset(s)
C.2.3 Grounds based on lack of significant therapeutic benefit
PART D – Paediatric Investigation Plan
D.I Existing Data and Overall Strategy Proposed for the Paediatric Development
D.I.a Paediatric Investigation Plan indication
D.I.b Selected paediatric subset(s)
D.I.c Information on the existing quality, non-clinical and clinical data
D.II Quality Aspects
D.II.a Strategy in relation to quality aspects
D.II.b Outline of each of the planned and/or ongoing studies and steps in the pharmaceutical development
D.III Non-clinical Aspects
D.III.a Strategy in relation to non-clinical aspects
D.III.b Overall Summary Table of all non-clinical studies
D.III.c Synopsis/outline of protocol of each of the planned and/or ongoing non-clinical studies
D.IV Clinical Aspects
D.IV.a Strategy in relation to clinical aspects
D.IV.b Overall Summary Table of all clinical studies
D.IV.c Synopsis/outline of protocol of each of the planned and/or ongoing clinical studies
D.V Timeline of Measures in the Paediatric Development Plan
PART E – Request for Deferral(s)
PART F – Annexes

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The resources required will depend on the applicant company's size and structure. In general, the core team should include at least a regulatory coordinator and an experienced medical writer, together with representatives from the CMC, nonclinical, and clinical functions, and a publisher to compile the submission package. While different functions may contribute materials for their subject areas, including texts that can be 'just added to the document' (beware, experienced medical writers will know that such texts invariably need extensive reworking), experience has shown that the medical writer's input is invaluable in ensuring consistency of content between the different sections. The medical writer's oversight is also essential for maintaining an overview of material still required and by when it will be needed if the envisaged submission date is to be maintained.

The submission date for the PIP application will usually be linked to one of the monthly PDCO meetings in the overall context of the anticipated date for the MAA submission, by which time a compliant PIP is required. Planning back from the MAA submission, it is prudent to plan for questions that will need to be addressed after initial submission of the PIP. Realistically, it can take at least 6 months between submitting the PIP and obtaining agreement on the paediatric measures contained therein. The time taken to prepare the PIP will depend on the resources available and the extent of information to be included. Even when a project is well resourced, considering the time needed for literature searches, obtaining advice on the paediatric strategy, authoring, at least two rounds of review, finalization, and compilation (including annexes in Part F), a time frame of around 6 months is realistic for preparing a submission-ready PIP. Thus, the time between starting to prepare a PIP and obtaining agreement from the PDCO can easily extend to a year (sometimes longer).

### Summarize information on the drug and the intended indication

In Part B, the applicant has to provide background information to support the rationale for the proposed paediatric strategy described later on in Parts C and D. The most challenging part to write is generally Part B.1, which provides information on the disease to be treated and the expected performance of the drug (or class of drug). Specifically, the guideline stipulates information on known and expected similarities and differences between adult and paediatric populations, and

Table 2: Categorization of the paediatric population according to the ICH E11 guideline

Paediatric category	Age
Preterm newborn infants	Preterm
Term newborn infants	0–27 days
Infants and toddlers	28 days to 23 months
Children	2–11 years
Adolescents	12–16 or 18 years, dependent on region

between different age categories within the paediatric population (e.g. as suggested by the ICH E11 guideline, see Table 2). Topics to be covered include characteristics and seriousness of the disease, prognosis, epidemiology, the drug's pharmacological properties and mechanism of action, and known or expected safety and/or efficacy information related to the mechanism of action. Phase I clinical pharmacology data should be included in Part B.1, but safety and efficacy data for the drug from clinical studies in adults should be summarized in Part D.

Bearing in mind that the paediatric population is highly diverse, the difficulty often encountered by writers is obtaining the appropriate information for Part B.1 to cover all age categories. In terms of disease characteristics and epidemiology, a literature search is often required, which can be time-consuming and therefore expensive. At kick-off meetings for PIPs, it is not unusual for medical writers to be told something like 'all the information is available in the Investigator's Brochure'. This is rarely, if ever, the case. The medical writer is therefore often left needing to educate the team about this important section, the purpose it serves, and, depending on the indication involved, the often considerable effort needed to research the relevant information and summarize it at the appropriate level for a PIP.

### Position the drug in the spectrum of therapeutic options

In Part B.2, a review of current methods of diagnosis, prevention, and treatment in paediatric populations for the disease at hand is required. Again, this section might require some literature search as well as consultation of regulatory information and drug approvals, as available on the Internet. The key elements to be summarized include current treatments and standard of care options across the entire paediatric population and how the applicant's drug compares with these options. If applicable, information in this section would also be used to

justify the options for active comparators in the proposed clinical studies.

Against the background of the information in Parts B.1 and B.2, the applicant has to provide a justification in Part B.3 for the anticipated therapeutic benefit of the drug. The key questions here are whether the drug is expected to provide improved safety or efficacy compared to current therapeutic options in some or all of the paediatric population, or whether comparable efficacy or safety are expected but with an improvement in quality of life due to, for example, an improved dosing regimen or an age-appropriate mode of administration.

### **Provide a convincing rationale for the paediatric strategy**

Supported by the considerations in Part B, the applicant will need to crystallize a paediatric strategy that is acceptable to the PDCO. A primary aim of the Paediatric Regulation is that clinical studies should be designed and conducted to provide paediatric data that can be used as the basis for the drug's prescribing recommendations. However, depending on the type of drug, the nature of the disease, and the epidemiology of the disease across the paediatric population (i.e. as described in Part B), the applicant may instead decide upon a strategy that includes proposing a waiver and/or a deferral for measures in some or all of the paediatric population. A waiver (to be described in Part C) means that the applicant proposes not to conduct paediatric measures, i.e. clinical or nonclinical studies, or testing of an age-appropriate formulation. A deferral (to be described in Part D) means that paediatric measures are proposed but that their completion and reporting are to be delayed, generally with respect to the timing of an MAA submission for adults.

In some cases, a waiver for the class of drug (as published by the EMA) may be applicable and the applicant can refer to this in the rationale for not conducting paediatric studies in some or all age categories, or for specific indications. This does not absolve the applicant from submitting a PIP, even if a class waiver covers all age categories. Class waivers published by the EMA are typically available for drugs used to treat diseases occurring only in adults, or where there is reason to believe that the class of drug is unlikely to have adequate efficacy or safety in paediatric patients. In addition, product-specific decisions published by the EMA may also provide insight from similar types of drugs with regard to whether a waiver may be appropriate for the applicant's drug.

Waivers will only be granted by the PDCO when the applicant can make a convincing case that paediatric measures are not warranted. An applicant's lack of interest in conducting a development programme for some or all of the paediatric population is not an acceptable reason for proposing a waiver.

The application for a deferral is product-specific and is generally driven by practical considerations such as availability of an age-appropriate formulation of the drug, the need for further nonclinical studies, or the requirements of a global clinical development strategy (e.g. driven by the availability of data from other regions).

A common situation is that the applicant proposes paediatric measures for at least part of the paediatric population, and a waiver for the remainder of the paediatric population. For the writer the challenge is to craft a convincing rationale for the design of these measures that harmonizes with the background information provided in Part B. This is not trivial because there is often an inherent tendency by applicants to propose a minimal number of measures, and such an approach may be difficult to align with the information provided in Part B and may also contradict the PDCO's somewhat academic approach to the need for paediatric measures. The result is that rationales for waivers (in Part C) and proposed paediatric measures (in Part D) usually result in a high degree of iteration between the medical writer and other team members over a period of several weeks before the texts are agreed upon by all. To a lesser extent the same is also true for the rationale for a deferral provided in Part E.

In Part D of the PIP, which is the core of the 'plan' being proposed, the descriptions of the paediatric measures to be conducted are preceded by summaries of existing information relevant to the drug's formulation and its nonclinical and clinical development. In terms of clinical development, this section should provide an overview of existing data on the efficacy and safety of the drug obtained in clinical studies in adults. However, clinical pharmacology data should not be provided here because this information will already have been summarized in Part B.1 in the context of the drug's pharmacological properties and mechanism of action. If necessary, cross-references back to information summarized in Part B should be used.

The paediatric measures being proposed, in terms of 'quality' (e.g. development of an age-appropriate formulation) and nonclinical as well as clinical studies, need to be specific in terms of

strategy and method descriptions (the EMA provides a PDF template for synopses of nonclinical and clinical studies) as well as timelines. Here the writer is often confronted with the team's desire to be as noncommittal as possible. However, anecdotal evidence consistently suggests that the PDCA requires specific descriptions of measures that may be conducted several years in the future, including details of statistical analyses. Furthermore, the timelines for all proposed measures need to be specified in relation to the submission date for the MAA. The timelines have to be defined to at least the nearest quarter year and are binding, meaning that after agreement on the PIP has been obtained they may only be changed via the laborious procedure of a PIP amendment. The details of the paediatric measures and their timelines are usually the subject of intense discussion within the team. The writer can play an important role in ensuring that the measures being proposed are aligned across different functional areas and within the overall context of the background information on the drug and the disease presented in Part B.

### Complete the PIP package

Even after the team has reached an agreement on the content of Parts B–E, time still needs to be planned in to complete the PIP package through to submission readiness. This is the time when the content is now stable and the writer can finalize technical issues such as formatting, cross-referencing, and consistency of language. There are also a number of technical requirements specified by the EMA that need to be taken care of, such as removing active hyperlinks to references or tables and figures, and ordering the list of published literature at the end of the PIP alphabetically.<sup>3</sup>

The annexes in Part F will also need to be completed during this time. In addition to providing copies of all published literature referred to in Parts B–E, the annexes should also include other relevant reference materials where available, such as an Investigator's Brochure, a Risk Management Plan, product information if the drug is already approved, any opinions and/or decisions received for the drug from regulatory authorities, and any official scientific advice

received on the drug. Although the annexes should ideally be compiled as far as possible while the PIP texts are being drafted, in practice a large part of this task is often completed shortly before submission and careful planning is needed to avoid this becoming a rate-limiting step. The services of a publisher are required for electronic compilation of a PIP submission, and in practice the medical writer also acts as an interface between the publisher and the rest of the team for resolving last-minute issues before the PIP application is ready for submission.

### Conclusions

The PIP is a relatively new type of regulatory submission document that many applicants still have little or no experience of preparing. Depending on the drug and the disease at hand, the PIP can be a demanding document to write and the effort required in its preparation is often underestimated. An experienced medical writer can play a key role in helping applicants interpret the requirements of the PIP guideline so that team members can provide the required material and scientific guidance needed for writing the various sections of the PIP. Ultimately, by interacting proactively with the applicant's team, the medical writer's goal should be to ensure that the PIP application is as clear and focused as possible so that only a minimal number of issues for resolution are raised during its review by the PDCA.

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## Author information

**Douglas Fiebig** started his career as a medical writer at Hoechst in 1996, after receiving his PhD in environmental microbiology and spending several years in academic research. After the company went through several mergers, culminating in the formation of Aventis, Douglas and two colleagues co-founded Trilogy Writing & Consulting in 2002. The focus of his work has been

writing for regulatory submissions in all major pharmaceutical markets. Douglas has been involved in preparing Paediatric Investigation Plans (PIPs) since they became mandatory in 2007. He regularly runs workshops on the practicalities of writing PIPs for EMWA and other organizations, and currently serves in the EMWA Professional Development Committee.

## Pharmacokinetics series Children are not 'small adults'

For many years the therapeutic drug dose in children was determined by simply making a proportional adjustment of the adult dose based on the weight of the child relative to the adult. The view that children are just 'small adults' has been debunked by a greater understanding of physiological and biochemical ontogeny and the pharmacological differences that can occur in children compared with adults. Developmental changes in the 4 main pharmacokinetic (PK) processes, absorption distribution, metabolism and elimination (ADME) have been noted. For example changes with age in the absorptive surface areas such as the gastrointestinal tract, skin and lungs can influence the bioavailability of a drug. Generally clearance mechanisms in infancy and early childhood are inefficient. The drug metabolising enzyme cytochrome P450 1A2 (CYP1A2) is absent in neonates therefore they are unable to metabolise caffeine to paraxanthine. Adult levels are only reached after 1 year of age. CYP2C9 (which accounts for approximately 20% of oxidative drug metabolism) activity increases from birth to 10 years of age whereupon it exceeds that of an adult, thereafter there is a decline to adult levels. Renal function as measured by glomerular filtration rate develops with age. Adult values are generally reached by 1 year of age. Genetic variants of ADME genes, different disease phenotypes, disease progression, and concomitant treatment all contribute to this variation.

The paediatric population is far from homogenous, variability is potentially larger than that observed in the adult population. Based on organ maturation, body weight and body composition children can be classified into at least 4 different population categories; neonates (birth to 28 days), infants (28 days - 23 months), children (2-11) and adolescents (12 to 16/18 years old)<sup>1</sup>. The challenge for the drug developer is to understand the heterogeneity and how this affects the pharmacokinetic/pharmacodynamic relationship and ultimately the therapeutic dose; is it sufficiently different to that found in adults to warrant a dose adjustment?

Presently around 70% of the medicines given to the paediatric population and 93% of the medicines given to critically ill neonates remain unlicensed or are used off-label<sup>2</sup>. The regulatory authorities have taken steps to address this imbalance. The EMA state that for all new chemical entities innovators must consider a paediatric investigational plan (PIP). In some instances a waiver will be granted where the disease is not present in

children, for example Parkinson's' disease. In all other cases a series of studies are required to investigate the quality, safety and efficacy of the drug in children to allow choice of the appropriate dosing regimens.

Estimating PK in children can be challenging, the mantra oft said is 'the need to do more with less'. Blood sampling for drug measurement is less extensive compared with adults (it's a volume issue!) and subjects tend to be fewer. This scenario lends itself to the use of population PK methodology<sup>3</sup>. Here data from all patients are analysed together and a mean set of population PK parameters (generally clearance and apparent volume of distribution) are estimated. The variability around these parameters can then be investigated in terms of the different age groups etc, within the paediatric population. A caveat with this technique is that to fully understand dose adjustment in each of these cohorts a sufficient number of patients needs to be investigated in each of the sub-groups of interest.

Understanding drug behaviour in children has great societal value. For new medicines it will result in the early licensing of innovative products for paediatric use. For existing drugs, the development of child appropriate formulations coupled with a greater understanding of the PK/PD relationships in children will increase the armamentarium of safe and effective medicines available to treat childhood disease.

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# ADHD: A true neurodevelopmental disorder?

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## Abstract

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders. First described in 1798 by Alexander Crichton, ADHD became widely known outside the medical profession with the publication of the story of Fidgety Phil ('Zappelphilipp') in Heinrich Hoffman's book 'Struwwelpeter' in 1846. Since then, scientists and clinicians have been struggling to understand its causes. To date, there is neither a genetic test nor a brain scan to diagnose ADHD due to the fact that it is a heterogeneous collection of behaviours that appear to have different causes and symptoms. In view of the lack of an objective diagnostic method, the major difficulty that specialists face is to decide where to set the threshold between behaviours and states of mind that require medication or behavioural treatment and differences that can be left alone. The increased rate in diagnosis and stimulant use in ADHD recently raises several issues, notably, are we setting lower diagnostic thresholds because of societies' intolerance of behaviours and impairments associated with ADHD? This article discusses some of the controversies in ADHD diagnosis and treatment, including many medical, social, and ethical aspects.

**Keywords:** Attention deficit hyperactivity disorder, ADHD, Impulsivity, Stimulant, Methylphenidate, Atomoxetine

Attention-deficit/hyperactivity disorder (ADHD) is a highly disruptive childhood-onset disorder, characterized by inappropriate hyperactivity, inattention, and impulsivity that onsets before the age of seven and often persists into adolescence and adulthood.<sup>1,2</sup> It is the most common neurodevelopmental disorder of childhood, estimated to affect

1.4–6% of school children, and probably the most controversial.<sup>3</sup>

The major clinical features are severe impulsiveness, lack of concentration, and motor hyperactivity, observed in at least two distinct settings, for example, home, school, and social settings. ADHD is often accompanied by other psychiatric and developmental disorders, including learning impairments, oppositional defiant disorder, conduct disorder, autism, and dyslexia.<sup>1</sup> These impairing symptoms put children at risk of education failure and can severely disrupt family, teacher, and peer relationships.

From a public health perspective, the cost of ADHD is significant in terms of academic underachievement, later unemployment, and often comorbid substance abuse and antisocial behaviour.<sup>4</sup> In England and Wales, children with ADHD place a significant cost on health, social, and education services, reaching £23 million for initial specialist assessment and £14 million annually for follow-up care. In 2006, the total annual cost of prescribed stimulants and other drugs for ADHD in England was roughly £29 million.<sup>5</sup> And the costs keep rising....

## Molecular genetics of ADHD

Given the impact of ADHD on society as a whole and particularly on children's quality of life, it is imperative to understand the aetiology and pathophysiology of this disorder. At present, little is known about either the causes or the mechanisms of ADHD, but family, twin, and adoption studies provided strong evidence that ADHD is hereditary.<sup>1,6</sup> Twin studies showed that disease concordance was much higher in identical twins compared to non-identical twins, with 60–90% of the phenotypic variance being explained by inherited factors. There is evidence for shared inherited

factors with a wide range of psychiatric disorders. Another interesting aspect is that ADHD prevalence is higher in males than in females, but at present a genetic explanation for this phenomenon is lacking.<sup>1</sup>

Interestingly, the high-heritability estimates are similar to those found in other psychiatric disorders such as schizophrenia and autism. As with these disorders, genetic effects are not 100%, indicating additional contribution from non-shared environmental factors, epigenetic effects, random events, or measurement inaccuracies. ADHD, like other common medical and psychiatric disorders, is considered a complex genetic trait, influenced by multiple genes, non-inherited factors, and the interaction between them.

With this high heritability, much effort has been, and still is being, directed towards searching for specific susceptibility genes. The search has consisted of identifying common DNA variation. Whole-genome linkage studies were not able to point to regions harbouring susceptibility genes, probably reflecting the fact that there are no common susceptibility genes of large effect sizes for ADHD.

Candidate gene association studies have been more promising, and a small number have been shown to consistently withstand replication and meta-analysis, including genes involved in the dopaminergic pathway, long hypothesized to be involved in ADHD; the 7-repeat allele of the D4 dopamine receptor gene (*DRD4*), a microsatellite repeat in the D5 dopamine receptor gene (*DRD5*), and a 480 bp variable number tandem repeat in the dopamine transporter gene, *DAT1*.<sup>1</sup> There is considerable sample heterogeneity reported for the *DAT1* allele, which could be the result of multiple polymorphisms in this gene. There is also evidence that the gene encoding a protein responsible for the degradation of dopamine (*COMT*) could have a modifying effect on the ADHD phenotype (reviewed by Thapar *et al.*<sup>7</sup>).

Genome-wide association studies are still at an early stage for ADHD and have provided some interesting genes to investigate further. However, all association studies have failed to find a common gene variant and have not provided support for previous candidate genes. This is probably a reflection of the extremely large sample sizes required for the small effect size expected and sample heterogeneity. Another possibility is that disorders such as ADHD may be better explained by the effect of rare genetic variants, for example, rare copy number variants (CNVs). CNVs are part of the normal variation of the human genome and are DNA segments of 1 Kb or

greater that vary in number when the genomes of different individuals are compared. They can be copy number gains (insertions and duplications) or subtractions (deletions) when compared to the control genome. Large and rare CNVs have been associated with neurodevelopmental disorders such as schizophrenia and autism.<sup>8,9</sup> A UK study analysing rare CNVs and ADHD found a significantly increased rate in ADHD cases compared to controls and also reported an overlap of CNVs found in ADHD with both schizophrenia and autism, further supporting ADHD as a neurodevelopmental disorder.<sup>10,11</sup>

Molecular genetic studies at best account for less than 5% of the estimated heritability in ADHD symptoms due in a large part to the heterogeneity of the clinical phenotype and the genetic architecture. Thus, future directions include finding ways of dividing subjects into more homogenous subgroups for use in genetic studies<sup>12</sup> and using intermediate phenotypes or endophenotypes. Endophenotypes are stable, heritable measurements that are closer to the biological aetiology of a disorder (e.g. the gene) than the clinical diagnosis itself. Examples of endophenotypes that measure simpler traits, likely to be influenced by a smaller number of genes, are magnetic resonance (MR)-based measured effects on brain structure.<sup>13</sup> Importantly, some MR imaging studies provide evidence for differences in brain structure and/or function that may facilitate linkage studies as well as provide neurobiological mechanisms for how gene variants impact on the brain.<sup>14,15</sup>

## Environmental impact on ADHD

There are a number of environmental risk factors that have been associated with ADHD. Major associations have been seen with maternal-related prenatal risk (alcohol, smoking, drug use, stress in pregnancy), pregnancy and birth complications, including prematurity and low birth weight, and environmental exposures, including toxins (pesticides, polychlorinated biphenyl, and lead) and some virus infections. At present, although some studies have found positive association with an agent and ADHD, for example, an association between low-level prenatal organochlorine exposure and ADHD-like behaviours in childhood,<sup>16</sup> no firm conclusions can yet be made for a link to ADHD behaviour outcome, with the exception of extreme situations including extreme prematurity, very low birth weight, and foetal alcohol syndrome. Similarly, despite many studies of diet and ADHD symptoms, there is no evidence yet to show that

diet plays a causal role, although some nutritional changes may help relieve some symptoms in children diagnosed with ADHD (see below). Adverse social and family environments have also been associated with ADHD, but none so far have been found to be causal, with the exception of children exposed to extreme early deprivation: the Romanian orphans who were studied after their adoption in the UK and were found to have a deprivation specific ADHD-like behaviour (reviewed by Thapar *et al.*<sup>7</sup>). Surprisingly, a study of television and video game use (whether total time spent or exposure to violent content) did not predict attention problems or influence school grades.<sup>17</sup>

### No gene, no real disease?

At present, there is no single cause of ADHD, and identified risk factors are non-specific, as most of those found appear to affect a range of different neurodevelopmental and psychiatric phenotypes. The lack of common susceptibility genes/loci and the difficulties in a clear-cut diagnosis have led to debate in the scientific and medical community about ADHD aetiology, including a view from Szasz, who has argued that ADHD was ‘invented (by psychiatrists to give a medical explanation for antisocial human traits) and not discovered (behavioural interpretations do not represent a disease)’.<sup>18</sup>

Some believe that ADHD is selected for in evolution, for example, Hartmann, who developed the hunter-farmer theory of ADHD.<sup>19</sup> Building on this, Jensen regards ADHD as a ‘disorder of adaptation’ and suggests that ‘many emotional and behavioural responses (particularly if relatively commonplace

within a given species) may not just be ‘symptoms’ of disorders, but they might instead reflect adaptive responses of the organism to environmental demands’.<sup>20</sup> Gallagher goes even further to suggest that ADHD may have evolved because it increases creativity and inventiveness of the population and that ‘if ADHD genes are selected for because they foster creativity, then ADHD is not a neurological ‘defect’, but rather a variant temperament (albeit one which may require intervention)’.<sup>21</sup>

Eisenberg provides evidence for the selection of an associated ADHD variant from a study of Ariaal men of northern Kenya, where the ADHD-associated allele of the *DRD4* gene promotes behavioural/psychological traits that are helpful in some social and ecological contexts, but detrimental in others.<sup>22</sup> Williams and Taylor<sup>23</sup> conclude from a study using a neuropsychological test (simulations of the changing food group task) that ‘even individually impairing combinations of genes, such as those that may cause ADHD, can carry specific benefits for society, which can be selected for at that level, rather than being merely genetic coincidences with effects confined to the individual’.

Adherents of another theory, the social construct theory, believe that society has created ADHD by its specific demands on children and its perception of an individual group (see debate Timimi vs. Taylor),<sup>24</sup> and the neurodiversity theory proposes that ADHD is a normal human difference to be tolerated and respected as any other human difference.<sup>3</sup> Other critics interpret ADHD as being the consequence of disturbances in the relationship between the primary attachment figure (usually the mother) and child, a view held by some



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psychoanalysts particularly in Germany, which usually leads to hot debates at congresses.

## Diagnosis

ADHD is usually diagnosed using the Diagnostic and Statistical Manual of Mental Disorders – 4th Edition (DSM-IV), which defines three general subtypes:<sup>25,26</sup>

1. Predominantly hyperactive-impulsive: a child who is excessively fidgety and restless, seems to always be ‘on the go’, and has difficulty waiting and remaining seated, acts immaturely, may not set physical boundaries, and may exhibit destructive behaviours.
2. Predominantly inattentive: a child who is easily distracted, forgetful, manifests day-dreaming, disorganization, poor concentration, and difficulty completing tasks.
3. Combined type.

However, there is mounting evidence that the ADHD/inattentive and ADHD/combined subtypes are separable disorders with different underlying pathology.<sup>27-29</sup>

The DSM-IV diagnostic criteria consist of two dimensions: symptoms and impairment, each with subtype-specific descriptions. Not only is a distinction between symptom and impairment often unclear,<sup>30</sup> but so is a symptom-based rating problematic due to the subjectiveness of judgements of what is ‘normal’ and ‘abnormal’ behaviour. Similarly, impairment is ambiguous and depends on the individual challenges and demands that patients face in daily life. Hence, assessment of behavioural characteristics is subjective and may be interpreted differently by different observers and in different cultures.<sup>26,31</sup> According to Rousseau *et al.*,<sup>31</sup> the literature does not provide a definite answer about the DSM-IV cultural validity in child psychiatry. On the one hand, it suggests that all diagnostic categories may be found universally. On the other, variations in prevalence rates support the hypothesis of a role for social and cultural factors in the diagnostic process, that is, the existence of diagnostic criteria biases. For instance, ADHD prevalence is higher in North America than in Europe, where the International Classification of Diseases – 10th Edition (ICD-10) diagnosis of ‘hyperkinetic disorder’ is more commonly used. In fact, diagnostic criteria of ADHD in DSM-IV and ICD-10 are heterogeneous, and a positive ADHD diagnosis is three to four times more likely with DSM-IV than with ICD-10.<sup>32</sup>

ADHD often coexists with other conditions, and this makes its diagnosis more difficult. As many as one-third of children with ADHD have one or more co-morbidities, of which learning disabilities, oppositional defiant disorder, conduct disorder, anxiety, tics, and depressive disorders are the most common.<sup>26,33</sup> Most of these disorders share common features, e.g. similarity in symptoms or age at onset. There are currently no biomarkers of ADHD that could help diagnosis and assessment of treatment efficacy. Nevertheless, it is important to recognize the limitations of the DSM-IV definitions by adding more objective means of assessment to the diagnostic process.<sup>26</sup> Berger<sup>26</sup> has pointed to the need to verify the DSM-IV diagnostic criteria of ADHD in a more specific way, which will take into account gender, cultural bias, and developmental variations.

Some rating scales have been developed to specifically assist diagnosis, score symptom severity, and rate improvements in various domains during intervention, both in primary care and clinical trial settings. The most widely used are: ADHD Rating Scale, Conners’ Parent and Teacher Rating Scales, Child Behaviour Checklist, Parent-rated Hyperactivity/Impulsivity Swanson Nolan and Pelham Ratings, and UPPS Impulsivity Scale.

## Pharmacotherapies

There are pharmacological and non-pharmacological treatments for ADHD for both children and adults.<sup>34</sup> Pharmacological approaches are the most common and typically consist of stimulant medication, such as methylphenidate, dexamethylphenidate, mixed amphetamine salts, and lisdexamfetamine dimesylate. However, non-stimulants such as atomoxetine, clonidine, guanfacine, and reboxetine have also been found to be efficacious in treating ADHD, although their efficacy seems to be slightly lower than that of stimulants.<sup>35,36</sup> Among the different substance classes, there is a large variety of delivery forms (liquid, sprinkle, tablet, capsule, or patch), formulations (active isomers, mixtures of active and less active isomers, or prodrugs), and release forms (immediate-, intermediate- or extended-release).

Adverse effects are a serious problem compromising treatment compliance for both stimulant and non-stimulant medications.<sup>37</sup> The most common side effects of stimulants are decreased appetite, sleeplessness, headache, abdominal pain, and nausea,<sup>38,39</sup> whereas those of non-stimulants include decreased appetite, abdominal pain, vomiting, headache, sleepiness, and sedation.<sup>39-41</sup>

Adverse effects on blood pressure, heart rate, and exercise parameters have also been reported for both stimulant and non-stimulant drugs, but usually do not reach clinical relevance.<sup>40–44</sup> For instance, small but statistically significant changes in blood pressure and heart rate were observed at 6 weeks of treatment with high doses of extended-release methylphenidate in adolescents, without clinically meaningful changes in electrocardiogram and no serious cardiovascular adverse events.<sup>42</sup> Although rare, serious cardiovascular adverse events (e.g. vasculopathy) have also been reported with stimulant use.<sup>45</sup> No cytogenetic side effects have been associated with the use of methylphenidate.<sup>46</sup> A black-box warning for suicidal ideation has been published in the US prescribing information of the non-stimulant atomoxetine, based on findings from a meta-analysis showing that the drug is associated with a significantly higher incidence of suicidal ideation than placebo.<sup>40,47</sup>

Since ADHD medications are prescribed for long-term treatment, there is a need for longitudinal safety studies.<sup>37</sup> For instance, despite the frequent use of stimulants, there is still a lack of clarity on the effects of long-term use on growth and nutritional status of children.<sup>48</sup> As clinical trials in the paediatric population are limited, clinicians and health authorities must rely on spontaneous reports as the main source of information about previously unknown adverse drug reactions.<sup>37</sup> A recent systematic review of the safety information contained within the summaries of product characteristics (SPCs) of medications licensed in the UK for treating ADHD reported significant differences between the SPCs and national guidelines on prescription, partly due to the ongoing reactive process of amending the SPCs as new information becomes available.<sup>49</sup> This may confuse clinicians seeking advice on drug prescription for their ADHD patients.

## Alternative treatments

Complementary and alternative approaches are also used to ameliorate ADHD symptoms or combat its causes.<sup>50</sup> They include dietary modifications (diets rich in low glycaemic index carbohydrates, proteins, and essential fatty acids), nutritional supplementation (e.g. with essential fatty acids, vitamin B6, magnesium, zinc, L-carnitine, and different amino acids), herbal medicine (e.g. rhodiola, chamomile, and St John's wort), homeopathy, and physical exercise. Some of them have proven to be beneficial in ADHD patients.<sup>50</sup> Although the biological rationale for using them is clear from the possible causes of

ADHD and their relationship with diet, an objective assessment of their efficacy is difficult, a problem inherent to all dietary studies, not to forget the placebo effect.

A systematic review of 34 studies published in the Chinese literature found that traditional Chinese medicine (TCM) may have equal or better effectiveness than methylphenidate, but the quality of the clinical trials does not support any particular recommendation of TCM for treating ADHD in children.<sup>51</sup> Over the counter products used in Western medicine include *Ginkgo biloba* and short-chain fatty acids, but these substances have not been shown to be significantly superior to placebo or methylphenidate.<sup>52,53</sup> In a small, placebo-controlled trial, omega-3/omega-6 fatty acids improved symptoms in a sub-population of children with ADHD of the inattentive subtype and co-morbid neurodevelopmental disorders.<sup>54</sup>

In addition to medication, there are also non-pharmacological treatments. These are alternatives for patients who cannot or must not take the required medicines to adequately manage their disease, for instance because of contraindications and co-morbid conditions (e.g. anxiety and tic disorders), drugs' adverse effects, non-responsiveness, or reduced efficacy. Also, patients at risk of substance misuse should avoid stimulant medication. Alternative treatments include different forms of psychosocial interventions, e.g. cognitive and behavioural therapies. For instance, parent and teacher training in effective behaviour-management techniques – behavioural parent training programmes – may help reduce the problem behaviours associated with ADHD in children, and cognitive behavioural therapy is commonly used for adults with ADHD. Neurofeedback has also been proved efficacious in the treatment of ADHD, with a large effect on inattention and impulsivity and a medium effect on hyperactivity.<sup>55</sup> Computerized training of working memory is also beneficial, but current consensus is that the non-pharmacological therapies listed above are supportive for ongoing pharmacotherapies and should not be regarded as substitutions. However, this conception is controversial.

## Pill or therapist?

The choice of treatment, whether pharmacological or psychosocial, is multifactorial. Brinkman and Epstein<sup>56</sup> found that, at the time of diagnosis, parents and children view psychosocial treatment as a more acceptable option than medication, and that medication acceptability is significantly higher

among Caucasian than among non-Caucasian parents. Also, actual experience with medication can increase parent-reported acceptability of medication treatment for ADHD. However, acceptability alone does not predict implementation and adherence, neither of psychosocial nor of pharmacological treatment. Both are influenced by a variety of factors, for instance, the former by service availability and feasibility of family attendance (e.g. time and affordability) and the latter by perception of needs and benefits weighed against side effects and costs, patient acceptance, and social support. The choice of treatment also depends on the type and severity of symptoms presented and the respective perceived needs of patients and their families. Treatment preferences are often dynamic and context-dependent, as family priorities and values change over time. It has been noted that pharmacotherapies alone are better in the short term, but cognitive and behavioural therapies deliver the best results in the long term. It is also worth noting that ADHD medicines do not have disease-modifying potential, that is, they only bring symptomatic benefits for as long as the therapy lasts.

### Concluding remarks

As described above, ADHD is a controversial disorder for various reasons: its cause is unknown, its diagnosis subjective and the long-term efficacy and safety of its treatment are unclear. But is the mixture of complex aetiology and heterogeneous diagnostic criteria enough to refute its existence as a clearly identifiable and genuine neurodevelopmental disorder? Furman<sup>57</sup> argued in 2008 that evidence for a genetic or neuroanatomic cause of ADHD is insufficient and that ADHD is unlikely to exist as an identifiable disease. 'Inattention, hyperactivity and impulsivity are symptoms of many underlying treatable medical, emotional and psychosocial conditions affecting children', he says. Critics have described ADHD as a diagnosis used to label difficult children who are not ill but whose behaviour is at the extreme end of the normal range.<sup>58</sup> Controversy also continues to grow over medicines used to treat ADHD, their efficacy, tolerability, safety, long-term effects, and abuse potential, as well as social and ethical issues on ADHD diagnosis and treatment.

Are the arguments against ADHD being a real clinical condition still valid taking into account the most recent findings in genetics, pathophysiology, and neuroimaging? Even if yes, does this view help relieve suffering of symptoms and impairments

in ADHD patients? How can an unidentifiable disease be treated? Will the impact of undiagnosed ADHD on children's daily living in family, school, and social settings ever be measured? What is the psychological burden of parents believing that the abnormal behaviour of their children is biologically not explainable? Is ADHD a by-product of poor parenting or miseducation? The debate continues.

Singh noted that ADHD has served as a case study to illustrate the potential social and ethical consequences of psychiatric diagnosis and treatments; or macrolevel analyses of corporate, governmental, and institutional interactions that inhere in the take-up of psychiatric diagnosis and drug treatments.<sup>59</sup> She argued that neither bioethics nor sociology has yet managed to fully take on the complexity of ADHD. There is little attention to ADHD as a lived experience in local contexts, and this is particularly problematic because 'children carry this diagnosis in the midst of complex and highly contested social, political and medical territories', she says. The consequences of diagnosis for children's overall well-being have been neglected in scientific research, and much attention should be drawn to children's perceived experience of living with ADHD.

In contrast to the occasional denial of the existence of ADHD as a clinical entity, there is the risk of overdiagnosis and overtreatment, which refers to children who are diagnosed with ADHD but should not be (false positives). Global use of ADHD medications rose three-fold from 1993 through 2003, whereas global spending (2.4 billion US dollars in 2003) rose nine-fold.<sup>60</sup> Use and spending grew in both developed and developing countries, but spending growth was more pronounced in developed countries. In the United States, the number of physician outpatient visits, in which ADHD was diagnosed, increased by 66% (from 6.2 to 10.4 million) from 2000 to 2010.<sup>61</sup> Sciutto and Eisenberg<sup>62</sup> reviewed prevalence studies and research on factors affecting diagnostic accuracy in ADHD until 2007. They concluded that 'there does not appear to be sufficient justification for the conclusion that ADHD is being systematically overdiagnosed'. Nevertheless, they noted that this conclusion is generally not reflected in public perceptions or media coverage of ADHD. On the other hand, there are also misdiagnosis and underdiagnosis. For instance, girls are likely to be underdiagnosed because they more often suffer from the inattentive subtype without the disruptive hyperactive behaviour.<sup>48</sup>

If left untreated, ADHD may persist into adulthood and be accompanied by a variety of

behavioural, social, and economic problems, including depression and anxiety disorders, antisocial behaviour, poor peer relationships, substance abuse/misuse, learning disabilities, low academic attainment, unemployment, etc. Substantial progress continues to be made in our understanding of the aetiology and pathophysiology of ADHD resulting particularly from genetics, neurophysiological, and neuroimaging studies. This may help us not only to improve diagnosis and treatment of this impairing disorder, but also to develop and implement preventive strategies in the near future. In view of the increasing numbers of diagnosed ADHD cases recently, such improvements will have a large impact on health economics globally.

After a critical analysis of the literature, whatever ADHD represents for us, the often heartrending stories from those diagnosed with ADHD and their relatives underline the necessity to understand the pathogenesis of ADHD to develop effective preventive and symptomatic interventions.

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# Medicines information for patients: Insights into research and practice for medical writers

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## Abstract

Many people do not take their medicines as prescribed, and medicines can cause harm if not used appropriately. In addition, in most health systems there is increasing discussion about involving patients in decisions about their health – including decisions about the medicines they use. In addressing these issues, medicine information for patients can play a key role in supporting patients to get the best out of their medicines. For the information to work, it needs to be both accessible and understandable – this is easy to say, but less easy to put into practice. This article draws on research and practice to help answer the questions:

- Why is medicines information for patients so important?
- What sort of medicines information do people want?
- How can we write and deliver such information?

**Keywords:** Medicines information, Patient empowerment, Patient leaflets, User testing, Readability, Risk communication

## Why is medicines information for patients important?

Medicines are the most common intervention in developed health systems and up to half of people taking long-term medicines do not take them as prescribed.<sup>1</sup> In addition, medicines are one of the most common causes of harm in healthcare. Information for patients about their medicines can impact on both these areas.<sup>2</sup> Such information is also important because decisions about taking a medicine are one of the most obvious applications of the promotion of choice and decision-making in health – a move gaining ground across the developed

world. In the UK, a recent government policy document adopted the mantra of patients organisations, i.e. ‘no decision about me without me’.<sup>3</sup>

### European Union legislation

Importantly, medicines are one of the few healthcare interventions where patients routinely receive a piece of legally mandated information; the PL. In European Union (EU) legislative terms, PL stands for ‘Package Leaflet’. In this article I shall use the more appropriate term ‘Patient Leaflet’. This comprehensive leaflet, written and supplied in the medicine pack by the manufacturer, has been mandated since 1999,<sup>4</sup> with subsequent legislation requiring testing of the leaflets coming into force in 2005.<sup>5</sup> I use the term ‘comprehensive’ leaflets advisedly, as the patient leaflets are indeed comprehensive, with everything in the Summary of Product Characteristics (SmPC) included, but ‘in a form understandable to the patient’. As a consequence of reflecting the SmPC, the leaflet is largely about negative aspects of the medicine, i.e. contraindications, precautions, and side effects.

The introduction of the testing of patient leaflets in the EU was a game changer because without a successful and documented test, no licence for a new medicine will be now granted. The testing is often referred to as ‘readability testing’ but the wording in the relevant directive is ‘The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use’. Guidance associated with the Directive describes a process called ‘user testing’ as one of the methods that can be used.<sup>6</sup> In practice, most testing uses this method, developed in Australia by Professor David Sless.<sup>7</sup> It is a type of performance-based testing: can potential users find and understand key points of information for safe and effective use? There are two components to the testing. The first is quantitative – how many can find and understand key points? The second is

qualitative; open questions about what people find useful and not useful. I will describe this process in more detail later.

#### *Partnership in medicine taking initiatives*

Alongside the development of legislation about medicines information, a re-framing of why people don't take their medicines as prescribed has been taking place. In the UK in 1997 a landmark document developed the idea of improving medicine taking through a partnership approach with patients.<sup>8</sup> This was part of a sea change in thinking, with the notion that intentional non-compliance (a conscious decision not to take) is as important as unintentional non-compliance (where barriers stop people taking, such as forgetting). The thrust of the thinking behind this document was that if people are given the opportunity to take part in decision-making about their medicines, they might be more likely to take that medicine as agreed. More recently in the UK, official guidance has re-stated that approach: 'Addressing non-adherence is not about getting patients to take more medicines per se, rather it starts with an exploration of patients perspectives of medicines and the reason why they might not want or are unable to use them'.<sup>9</sup> The provision of appropriate information for patients is central to taking forward this approach.

### **What sort of medicines information do people want?**

Our thinking on going forward with research into medicines information for patients was shaped by focus groups we ran with people with asthma in the early 2000s.<sup>10</sup> We asked people what they thought about the medicine leaflets they received, and got some very straight answers: 'you throw them away don't you', 'they don't inspire you', 'things we want to know don't come first', 'priorities are those who wrote it, not patients' and 'people who suffer should help write leaflets'. More recently, we undertook a systematic review of the research published internationally on written medicine information for patients (for the UK Department of Health).<sup>2</sup> Alongside this review we undertook workshops with key stakeholders, including people who take medicines. Finally, as part of this work, we reviewed best practice in writing and information design, through analysis of key texts to produce guidance for people who write medicines information for patients.

The key findings were that, prior to 2006, most people did not value the medicines information they received, and there was concern about

complex language and poor visual presentation of information. Crucially people did not want written information as a substitute for spoken information from their health professionals. They valued the idea of information which is tailored and set in the context of their particular illness, and also information that contains a balance of benefit and harm information. The information design review of key texts (subsequently published separately<sup>11</sup>), came up with 10 principles, most of which will be well known to medical writers (see Box 1).

#### **Box 1 Ten ground rules for good document practice**

1. Short familiar words and short sentences
2. Short headings that stand out
3. Type as large as possible
4. Leave white space
5. Use bullets for lists
6. Be conversational
7. Use the active voice
8. Use non-justified text
9. Use bold lower case for emphasis
10. Pictures and graphs do not necessarily help

Adapted from: Raynor DK, Dickinson D. Key principles to guide development of consumer medicines information. *Ann Pharmacother* 2009;43:700-6.

### **How can we write and deliver such information?**

#### *Communicating side-effect information*

One of the most important points patients say they want to know about their medicines is about side effects – but in the past we have been poor at expressing this information. We have tended to use difficult medical words to describe side effects, have given only vague (if any) information about how likely they are to happen, and not enough about what to do if the patient should get those side effects. In terms of frequency, our research on the understanding of verbal terms such as 'common', 'uncommon', and 'rare' led to a change in EU policy with the revision of guidance on the use of such terms. We found that members of the public grossly overestimated the chance of side effects when using these terms alone.<sup>12</sup> Our research also showed that percentages confuse many people, including lack of appreciation of figures less than 1%. This has led us to the use of wording similar



to so-called ‘natural frequencies’, for example, ‘affects less than 1 in 100 people’. One approach is to combine words and frequencies, e.g. may have advantages, for example, ‘rare (affects less than 1 in 1000 people)’.<sup>13</sup>

### *Benefit information*

Although most medicine leaflets now include more detailed information about side effects, informed by the new EU readability guideline,<sup>14</sup> there is still a long way to go in providing ‘benefit’ information. If people are to make good decisions about their medicines, they need to be able to balance the ‘chance of benefit’ from taking a medicine with the ‘risk of harm’. The influential document ‘Always read the leaflet’ from the Medicines and Healthcare products Regulatory Agency (MHRA) supported this argument, saying that leaflets ‘are too negative, with insufficient information on the benefits of taking the medicine, making it difficult for the patient to assess risk versus benefit’.<sup>15</sup>

More recently, the EU draft legislation on ‘Information for patients’ included the sentence ‘The package leaflet shall include a short paragraph which sets out the benefits and potential harms of the medicinal product’.<sup>16</sup> Alongside this there is the latest template for patient leaflets (from the Quality Review of Documents (QRDs) group of the European Medicines Agency) which describes how information on benefits of treatment can be included.<sup>17</sup> However, this guidance talks about benefit information in very limited terms, such as how a medicine works, rather than any numerical values about likelihood of benefit.

This is an important distinction because, as we now present harm information numerically (e.g. ‘affects less than 1 in 100 people’), if we are really going to give people information to be able to make a balanced decision, then they need benefit information in numerical terms.

However, our research to-date suggests that including benefit information in numerical terms may pose problems. We presented people both in the UK and in Australia with patient leaflets with numerical benefit information about a medicine based on an anti-platelet medicine. This included information about how the medicine worked, the general benefits in terms of reducing the chance of heart attack and stroke, and the following numerical information (based on trial data):

- ‘If 100 people took this medicine for 2 years:
- 3 of them would be saved from having a heart attack
  - 1 of them would be saved from having a stroke’

The consensus was that the principal of including more benefit information was a good one. However, the presentation of numerical benefit information provoked strong feelings, and even disbelief and shock. Many struggled to understand the numerical information and some thought it was a mistake, as it was ‘too low’.

### *User testing*

As mentioned above, the most common way of implementing the EU Directive on ‘consultation with target patient groups’ was to adopt a process of ‘user testing’. This performance-based testing contrasts with previous content-based testing, such as readability formulae or the use of checklists.<sup>18</sup> It is based on how information performs, not what it contains. It assesses whether information can be found and understood by potential users of the medicine, in one-to-one interviews. It is worth noting that readability formulae are largely based on word and sentence length and readability depends on so much more. It is also worth noting that if you calculate the readability score for a piece of text written backwards, it will achieve the same score when written forwards (as it contains the same words and the same length sentences). Box 2 describes the key processes in user testing. A key point to note is that it is an iterative process: you test the information, identify problems, then you remedy those problems using research evidence and good practice in writing and design. Then you test again. Clearly, simply testing the information alone does not improve it – so the testing has to be married with expertise in good writing and design practice.

#### **Box 2 Key steps in user testing process**

1. Select 15 key points which are relevant to the safe and effective use of the medicine concerned
2. Design and pilot a questionnaire which tests finding each piece of information and then its understanding through expression in the participants’ own words or answering the question to a scenario
3. Recruit 10 or 20 people from the target patient group
4. Interviewed each participant individually, asking them to use the leaflet to answer the questions. (The target is that for each point 90% need to find the information, and 90% of those be able to show understanding.)

5. The interview concludes with open, qualitative questions about what they liked and didn't like about the leaflet. (Some regulatory authorities such as the MHRA place as much value on the qualitative questions as on the quantitative questions.)
6. The results are then analysed, identifying the questions that people struggled to find or understand, and looking at their general comments
7. The leaflet is then revised to remedy those problems, using research evidence and good practice in writing and design
8. Test again on a further 10 or 20 people
9. Analyse the results and if problems remain, go round the loop again.

### *Wider application of user testing*

User testing is highly versatile and can be applied to any leaflet format, e.g. large print leaflets, audio versions, and web-based medicines information. It can also be applied to other forms of information such as medical device 'Information for use'. This also includes materials produced by health services such as the booklet supplied in the UK to everybody who takes lithium. During development, the booklet was revised and went through two rounds of user testing, with many changes. This included the heading 'Risk factors for toxicity' becoming 'What can make the level of lithium in my blood get too high?', a good example of the use of conversational language in such materials. Clinical trial patient information sheets have also been tested and improved.<sup>19</sup>

We have also user tested the European Public Assessment Reports (EPAR) Summaries. The full EPARs describe the potential benefits and risks of a medicine and how the regulators came to the view that the benefits outweigh the risks. The EPAR Summary is a 'short lay version ... written in a manner understandable to the public' and designed to 'give the public adequate information to understand the basis for approval'. Our testing of both the web and hard copy version of an EPAR Summary found that only 25% of the points of information tested reached the performance levels set for leaflets. Qualitative questions showed considerable confusion about the purpose of the document. After revision and re-testing the number of points found and understood rose to between 70 and 80%. Qualitative comments on the original document included 'It's not user friendly

from the start. It's more like something from a lecture'. In contrast, talking about the revised version, one participant said 'It's in bullet points and easier to read than paragraph after paragraph of information'.

One example of applying user testing to materials for health professionals is our SmPC testing with doctors. It was no surprise to find that these documents tested poorly. The qualitative feedback was very instructive, with use of words like 'muddled' and 'information buried'. We went through an iterative process of testing four formats for SmPCs, with the final version performing much better than the one we started with. We will be forwarding the results of this research to the European Medicines Agency to inform current consultations on the future of SmPCs and package leaflets.

As with all information, one of the keys to the revised SmPC was clear signposting with good headings and sub-headings – the same approach as that which works for lay people. Other testing that we have undertaken has been with the educational materials supplied with Risk Management Plans in Europe and Risk Evaluation and Mitigation Strategy documents in the USA. This includes information for both health professionals and for patients, and it is very clear from this work that writing for health professionals really is the same as writing for patients – both want plain, clear, and easy to access information.

### **Key messages**

Recent trends in policy and practice, along with the research evidence which are described can inform how we go forward with medicines information for patients.

- As well as supporting safe and effective medicine taking, people need medicines information to let them understand the associated benefits and harms. This can then allow a more informed decision to be made.
- The risk of a side effect can be better described using a '1 in 100 people' format, rather than just verbal terms or percentages.
- Preliminary research suggests that the provision of benefit information numerically presents problems and further research is needed.
- User testing can, with small numbers of participants, help to identify problems in written medicines information. However, expertise in good writing and design is needed to resolve those problems.

- Experience with the revision and testing of materials with both patients and professionals suggests that the same principles apply – both want plain, clear, and easy-to-access information.

The Pharmacovigilance Directive of 2011<sup>20</sup> required the Commission to present a report ‘regarding the readability of the summaries of product characteristics and the package leaflets and their value to the healthcare professionals and the general public’ and that they should then make proposals for improvement ‘to ensure that they represent a valuable source of information for healthcare professionals and the general public respectively’. We hope that the findings of the research described above will contribute to that report.

### Declaration of interest

Professor Raynor is co-founder and academic advisor to Luto Research ([www.luto.co.uk](http://www.luto.co.uk)) which develops, refines, and tests health information.

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### Author information

DK Theo Raynor, PhD, FRPharmS worked in hospital pharmacy practice before becoming inaugural Professor of Pharmacy Practice at Leeds in 2000. Theo’s research focuses on effective delivery of medicines information for patients and he advises policy makers at national and international level. He is co-founder and academic advisor to Luto Research ([www.luto.co.uk](http://www.luto.co.uk)) which develops, refines and tests health information.

# The MHRA perspective on the new pharmacovigilance legislation

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Following an extensive period of drafting, consultation, negotiation, and re-drafting the new European Legislation came into effect in July this year. The new measures will be the biggest change to medicines legislation since the creation of the current European system in 1995. The background to the forthcoming changes dates back to 2003 when the European Commission decided to undertake an assessment of the pharmacovigilance system. Independent review and public consultation followed, as well as further work at the Commission, the European Medicines Agency (EMA) and EU member states, resulting in the publication of Regulation (EC) 1235/2010 and Directive 2010/84/EC on 31 December 2010.

The overriding purpose of the new package is to strengthen the public health system through better pharmacovigilance. All areas of post-marketing activities are subject to revision from ADR reporting, signal management, Periodic Safety Update Reports (PSURs), Risk Management Plans (RMPs) and Post Authorization Safety Studies (PASS).

As well as the public health angle the new legislation also seeks to improve efficiency by having improved decision-making processes, reducing duplication and making better use of IT through the use of centralized systems and standards.

However, not all of the new measures will come into effect immediately and a period of transition will apply in a number of areas.

Marketing Authorization Holders (MAHs) and other stakeholders should refer to the EC Implementing Measures and the Good Vigilance Practice Modules produced by the EMA and member states.

This article hopes to highlight areas of interest to medical writers, identifying what the major changes are and when they come into play.

## Implementing Regulation

The European Commission, working with the EMA and member states, has developed Implementing Regulation to provide essential technical details on what must be done by the national competent authorities (NCAs), MAHs and the EMA on the introduction of the new legislation. A concept paper on these measures was made available from 8 September to 7 November 2011 for consultation; following this, the revised Implementing Regulation was drafted in discussion with member states and formally adopted and published in the official journal as Commission Implementing Regulation (EU) No. 520/2012 on 19th June.

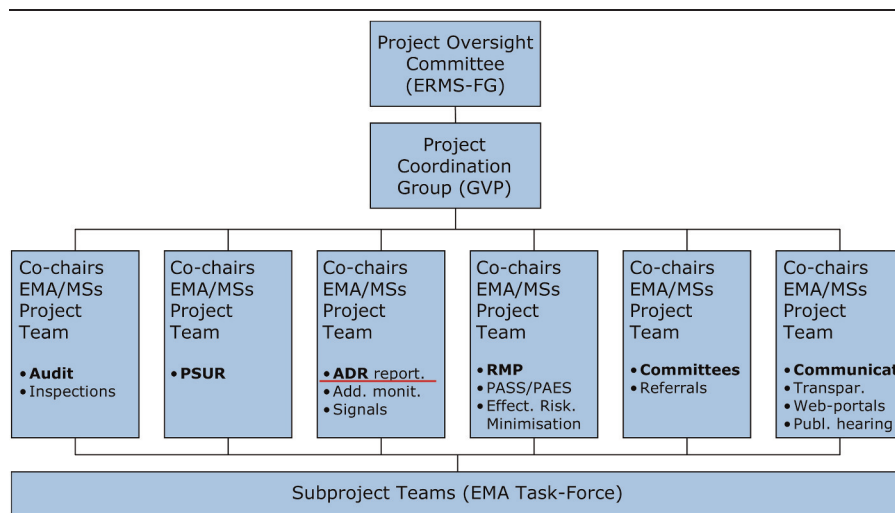
The Implementing Regulation covers the following key areas in the pharmacovigilance process:

- Pharmacovigilance Master File System (PMFS)
- Quality Management System
- Use of terminologies
- Adverse drug reaction (ADR) reporting and individual case safety report (ICSR) standards
- Format and content of PSURs
- Format and content of RMPs
- Format and content of post-authorization studies
- Signal management responsibilities.

## Good Vigilance Practice

Sitting beneath the Regulation, Directive and Implementing Measures are a set of Good Vigilance Practice (GVP) modules. The GVP modules replace Volume 9A and set out detailed, practical guidance on how MAHs and member states should meet the requirements. GVP is being developed according to the governance structure set out in Table 1; the

Table 1: GVP governance structure



concept is that the EMA and member states co-chair project teams to develop the guidance and report in to a project coordination group which in turn reports in to the European Risk Management Strategy Facilitation Group (ERMS-FG).

The first wave of GVP was released for consultation on 22nd February and adopted on 25th June, and covered:

- MODULE I Pharmacovigilance Systems and their Quality Systems
- MODULE II Pharmacovigilance System Master File
- MODULE V Risk Management Systems
- MODULE VI Management and Reporting of Adverse Reactions
- MODULE VII Periodic Safety Update Report
- MODULE VIII Post Authorization Safety Studies
- MODULE IX Signal Management.

Further waves are scheduled as follows:

III	Pharmacovigilance inspections	Q3 2012
IV	Pharmacovigilance system audits	Q3 2012
X	Additional monitoring	Q2 2012
XI	Public participation in pharmacovigilance	Q4 2012
XII	Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action, and planning of public communication	Q4 2012
XIII	Incident management (may be included in module XII: to be confirmed)	Q4 2012
XIV	Referral procedures for safety reasons (may be part of GVP or notice to applicants: to be confirmed)	Q3 2012

XV	Safety communication	Q3 2012
XVI	Risk-minimization measures: selection of tools and effectiveness indicators	Q3 2012

The MHRA is co-chair of Project Team 3, concerned with the development of GVP for ADR reporting, signal management, and additional monitoring. With regard to ADR reporting, it is known that centralized reporting to EudraVigilance will not be in place until after a period of transition while the functionality of the system is enhanced. This is likely to be in 2015 and until that time national arrangements will be in place. It is likely that some member states will not require national reporting and request MAHs send ICSRs to EudraVigilance, while others will have specific requirements for national, third country, and non-serious reports. The MHRA has specified that all UK ADR reports and serious third country reports are sent to the agency until the EudraVigilance functionality has been developed and audited. With regard to third country reports, our requirements will be kept under review as the Article 57 work takes shape and the EudraVigilance product dictionary is developed. MAHs should carefully review the GVP on ADR reporting to ensure the national requirements are clear.

There are other requirements for ADR reporting which MAHs need to prepare for that are set out in the GVP. These include the need to send non-serious reports, reports from patients, ADRs in post-authorization studies, and ADRs detected from digital media.

Another area subject to transition will be the reporting of ADRs identified in published literature. It was expected that the EMA would carry out monitoring and reporting to EudraVigilance on a

specified list of substances; however, this is now unlikely for some time and MAHs will need to continue reporting to NCAs as they currently do; again, GVP sets this out clearly.

## Signal detection

One of the major public health developments with the new legislation is that signal detection and signal management is a legal requirement on all parties. The GVP on signal management clearly sets out the requirements on the EMA, member states and MAHs. The guidance largely follows CIOMS VIII with the concept of signal detection, validation, prioritization, evaluation, and communication. MAHs will need to have documented processes for signal detection that are appropriate to the level of reports received and the portfolio of products. This may be individual case review, statistical analysis, or a combination of both. There is clear guidance of what and when to communicate signals with the authorities and when to respond to requests.

For member states there are similar requirements; together with clear roles in monitoring EudraVigilance, every substance authorized or registered in the EU will be appointed as a lead member state which will be responsible for generating and validating signals from EudraVigilance and the subsequent notification.

The MHRA considers this a vitally important aspect of the new legislation but, at least in the UK, it will not be in place of current practices but complimentary to the national PV system.

## Resources

While the EC impact analysis suggested minimum savings of €237 million per year, it is clear that

some of the savings will not be realized immediately and the period of transition will be somewhat longer than perhaps initially expected. MAHs will need to consider the implications of the Implementing Regulation, GVP and Article 57 to ensure they are adequately resourced to meet the new rules.

Member states are also considering the resource implications; as we are now working within the new system it is becoming clear we need to fully understand the resources required, particularly people and IT investment.

## Conclusion

As noted earlier, the new pharmacovigilance legislation is the biggest change to the European medicines regulations since 1995, and will deliver a much improved system for us to protect public health. The European Commission, EMA and member states have been working together over the past years to develop a comprehensive framework for us all to follow and this reaches across every area of the PV system. The above sets out just a few areas where the guidance is maturing; other aspects, such as PSURs, RMPs, PASS, and inspections will also need to be carefully considered by the industry. In addition, member states are also considering the implications for national reporting systems, the issues around public participation and communications, not to mention the new pharmacovigilance risk assessment committee, PRAC.

The work of the European regulatory network is intensifying and the challenges over the next few months will be significant. The rewards, however, in terms of an improved European pharmacovigilance system, promise to outweigh these challenges. The purpose of all of this activity is to benefit public health; this is what continues to drive us all.

# Are stem cells the future of healthcare?

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## Abstract

Stem cell technology holds a key, although arguably not an exclusive position, in the future of healthcare. Alongside two other candidates worthy of this mantle – personalized cancer medicine and vaccine development – all three healthcare innovations are explored primarily from a scientific and also an ethics perspective. This insightful and informative essay secured its 12-year old author a place on Newcastle Upon Tyne’s city universities’ ‘Leading Edge’ science programme in January 2012. The programme forges links between local academics and enthusiastic youngsters aged 12–14 years, selected from 13 participating schools. The aim is to motivate and inspire children to consider careers in science. Supported by their science teacher Jonny Instone, Gosforth Central Middle School’s team of six, including the author, worked with Dr Ben Horrocks from the University of Newcastle Upon Tyne’s Chemical Nanosciences Laboratories in the School of Chemistry. Their four-month nanotechnology project focused on the quantum dot and insights into its clinical applications. Project presentations took place at the city’s ‘Centre for Life’ in July 2012.

**Keywords:** Stem cell research, Individualized medicine, Vaccination

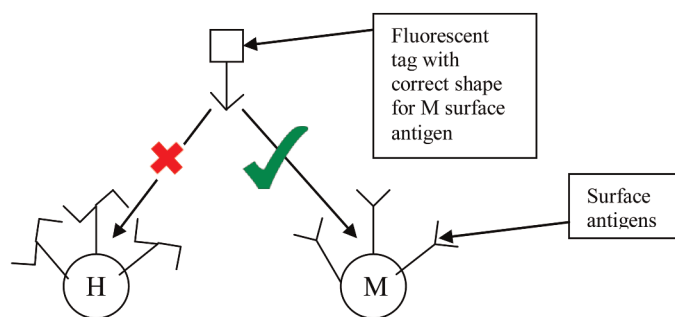
Stem cells are pluripotent (function in more than one way) cells that under the right conditions develop into any specialized cell in the human anatomy. This is a massive scientific breakthrough because if a patient has a dysfunctional liver they need not wait for a donor. An injection of stem cells into the failing liver will make new specialized liver cells. This is the theory. Many factors such as rejection and incorrect vascularization (production of new blood vessels from other blood vessels to feed a new tissue) can be fatal.

So, are stem cells the future of healthcare? There are other new treatments such as personalized

cancer medicine and large-scale vaccination in developing countries that serve different purposes but are also a big part of the future of healthcare.

When a sperm successfully fertilizes an egg, it divides into eight different embryonic stem cells, each one being identical to the other. These can then become different specialized cells, e.g. red or white blood cells because stem cells contain different genes needed to become any cell. These genes can be turned on or off by factors in the surrounding environment. The specialized cells then multiply to form a tissue or organ. Huge concentrations of stem cells are found in the umbilical cord because the growing embryo needs to develop tissues and organs.<sup>1</sup>

Early experiments in 2005 looked at patients with a muscle disorder. Scientists took a donor’s umbilical cord, collected the stem cells and placed them under the right conditions to create muscle cells. The steps were: removing the nucleus from the donor’s stem cell and adding the patient’s nucleus instead, successfully turning the stem cell into a mesenchymal precursor (this intermediate stem cell can be made into either a muscle, fat, cartilage, or bone cell) then adding appropriate tissue-specific stimulation to produce a muscle cell. To successfully make the muscle cell the scientist cocultured the cells with mouse feeder cells but could not give a mix of cells to a human because the human would not recognize the mouse cells and would reject them. So they had to remove the mouse cells. To make sure the scientist had successfully made a muscle cell from a stem cell they made a fluorescent tag which only connected with the muscle cell due to its unique surface antigens (each surface antigen has a different shape like a jigsaw piece that needs the other correct shape for it to fit into). Any cells that were not muscle cells were not tagged. When the cells were washed, only muscle cells kept the fluorescent tags. It was then possible to see the fluorescently tagged muscle cells using a special microscope (Fig. 1).



H, haemopoietic precursor cells – the intermediate stem cell for blood cell types; M, mesenchymal cells.

Figure 1: Diagrammatic representation of selective fluorescent tagging of mesenchymal cells.

It was important that all stem cells were converted to mesenchymal precursors and this was also checked using fluorescent tagging. Unconverted cells could start to proliferate (grow) and form a tumour/cancer cell. If injected into a patient they could become cancerous.<sup>2</sup> The scientists had made muscle cells to use in humans but these early experiments needed more work to make the cells safe by stopping rejection. Also, a way to make the new cells become a part of the patient's main tissue was needed.

Nowadays biomaterials science is used in stem cell technology to minimize problems with rejection and to make the new cells vascularize. Angiogenesis is the process that starts vascularization by producing the first blood vessels which helps make the 'scaffolding' needed to keep the cells working as one with the body. Also, materials science can help stop the rejection of the newly implanted cells by encasing them in a synthetic semi-permeable membrane through which the cells can secrete their products. The membrane does not allow the body's immune cells to attack the new cell inside it.<sup>3,4</sup>

In 2006, it was discovered in a mouse that cells – almost identical to stem cells – could be made from normal specialized cells. These stem cells are called induced pluripotent stem cells or iPSCs. These cells are created by a virus that causes the specialized cells to have almost the same characteristics as a stem cell but this virus can also cause a tumour which can lead to cancer. iPSCs are currently in their preclinical stage (tested on animals) but slowly progressing to clinical testing on humans.<sup>5</sup>

Stem cell research today is mostly at the pre-clinical stage with bone, blood vessels, and ligament engineering. So far, there have been no treatments able to cure a patient with no dangerous side effects. However, progress and discoveries continue.

In 2010, over one million litres of blood was collected in the UK from donors for blood transfusions. This is very expensive as every needle costs £1.50. Overall, this costs millions when added to the cost of paying the staff who take the blood. However, in 2011 scientists experimented up in Edinburgh and successfully grew red blood cells from stem cells on a small scale, *in vitro* (in the laboratory).<sup>6</sup> If this can be done on a larger scale in future, blood could be made to order.

Scientists of today predict that stem cells could influence treatments of conditions like: Parkinson's disease, Alzheimer's disease, diabetes, heart disease, stroke, cancer, and burns.<sup>7</sup>

There are many ethical issues with such complicated new technologies. Non-religious views state that an embryo is a living organism and therefore is entitled to some protection. This means that the cells taken out are entitled to their own protection and cannot be taken from that embryo for someone else to use. There are strict rules and regulations governing cloning of a human being using stem cells as any resulting cloned person may become confused and distressed due to his or her method of creation. Stem cells also have religious perspectives about how taking cells from another being is theft. Many Jewish followers believe that the world is incomplete and needs human interference for the world to 'work'. They believe one of the commandments was to heal in any way possible. This means they believe that using stem cells is right. Many Catholics in the 1960s strongly believed taking organs and transplanting them is a mutilation of the human body and thought this went against one of their beliefs, 'First do no harm.' Now they believe that it is charity and goodwill for someone to give up a precious organ for another human being.<sup>8</sup> This may mean that in future they may agree with the usage of embryonic stem cells, but as of now they are undecided.



Islamic law states that since the embryo is not a person, the extraction of embryonic stem cells does not violate any rules of the Holy Qur'an. However, the only humans who can use these cells are the couple who created them as the parents have the only rights to use them. On the other hand, the embryos can be cloned for therapeutic uses and the Islamic Institute allows embryos to be taken for research purposes. This means that stem cells can be taken from an embryo and used for research purposes but they cannot be transplanted into other patients.<sup>9</sup>

Personalized cancer medicine is an alternative to stem cells without as many ethical issues. Unfortunately, this medication is more expensive than stem cells and can only be afforded in modernized countries. Many types of the cancers respond differently when treated, so for example not all breast cancers can be treated with the same medicine. Surface antigens (or markers) on some types of cancerous cells allow scientists to create the 'missing jigsaw piece' or drug that fits into the marker and kills the cancerous cell. As surface antigens differ from person to person, the treatment is tailored to suit that person's cancer, hence the name personalized cancer medicine. Scientists can therefore identify the type of cancer a patient has before the doctor treats them. Drug companies developing new cancer medicines by law now have to develop a test kit for the cancer type at the same time as they develop the drug.

WIN consortium are a group of cancer experts trying to encourage cancer patients to participate in clinical trials for personalized cancer medicine. They have made a massive breakthrough with non-small cell lung cancer – a vicious killer – and have found that 5% of patients have a translocation – a point mutation (a point where the sequence in a gene has changed) – in the ALK gene that occurs in the cancer cell. This makes these patients good targets for the new drug. The drug has been tailored to find the patient's ALK gene and kill the cancer cell. This trial showed that 50% of patients with the gene translocation given the drug survived the cancer.<sup>10</sup>

Every year there are 14 million cancer sufferers worldwide so we need to tackle this. Personalized cancer medicine is at the same level of development as stem cell technology<sup>10</sup> and in the future they are both worthy contenders for the future of healthcare.

Another possibility for the future of healthcare is vaccine development.

Vaccines are much cheaper than both other technologies and are cheap enough for undeveloped countries. However, pharmaceutical companies

making these vaccines cannot afford to make them in sufficient quantities. Luckily, Bill Gates has enough money to develop vaccines and distribute them among developing countries. He has developed a malaria and typhoid vaccine, both killers in Africa, Asia, and Far Eastern countries.<sup>11</sup> These new vaccines are further developed than personalized cancer medicine and stem cell technologies. So is this the way forward?

For vaccines, scientists make a weakened microorganism which causes the disease they want the immune system to fight. Once injected into the body, the immune system creates antibodies that fight the microorganism. The immune system then remembers the microorganism in its 'immune memory' so when the vaccinated person comes into contact with the disease for real, their immune system remembers and fights off the disease.<sup>12</sup>

The Bill and Melissa Gates Foundation has funded the development of vaccinations for use in African children and babies. Currently, they are in clinical trials and 15,460 children and babies aged 6-12 weeks or 5-17 months of age were tested. The results show that after the first year of vaccinations, severe malaria went down by 50%. These are amazing results that the Gates Foundation is working hard to improve.<sup>11</sup>

With stem cells, personalized cancer medicine and vaccines, we can tackle three of the major causes of morbidity (illness) and mortality (death) in the world. All of these types of medicine are worthy contenders for the future of healthcare. Although vaccinations inhibit (stop) the patient having the disease in the first place if the patient did get cancer then they would require personalized cancer medicine. However, if the patient survived the cancer and lacked a particular specialized cell/cells, say a limb after a car accident, then stem cell technology would be required. All these technologies serve different purposes and therefore they all deserve a place in the future of healthcare.

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# O, safety, quo vadis?

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## Abstract

It is widely acknowledged that resolutions of difficulties tend to engender new problems. Increasingly, complex systems perpetuate increasing complexity. This discursive essay suggests that the most promising of discoveries, innovations, and inventions are impuissant to obviate once and for all the need for vigilance. For example, the pursuit of safety and prevention of contagion has burdened our societies with a variety of consequential expenses and environmental pollution. How reassuringly might infection control be achieved depends on the human element – on how attentively, thoughtfully are we as individuals able to meet challenges. The questions to be asked in solving any problem are: how much will a given solution cost and how reliable is it?

**Keywords:** Safety, Contagion, Infection control, Cost, Environmental pollution, Human element

Readers of *Medical Writing* would agree that ritual played prominently during the shamanistic-religious era of medicine. Perhaps less obvious is that ritualistic behaviours insinuate themselves even in contemporary scientific, evidence-based medical care – for lack of more sustainable alternatives, to indulge in the compulsion to appear militant in the face of peril, or for the sake of PC (procedural and political correctness) – and, with dismaying regularity, mindlessly.

I had repeatedly observed our surgery clinic nurses disinfecting a room after a procedure. One day, however, I became aware of an oddity in the process, and reached a dispiriting conclusion: the spectre of futility cannot completely be banished from our doings; we will *never* have absolute safety. Hands gloved, the nurses would spray disinfectants, and wipe surfaces clean (and, one hoped, bacteriologically safe) – performing more or less as they had been trained to. But then, still gloved, they would gather soiled linen and instruments, exit the room, and pull the door shut. In final analysis, the greatest protection they had provided was for themselves; yet even that not thoroughly, because later they would open the same door, turning the invisibly contaminated handle, but this time without gloves on.

The solution of a problem often delivers other problems. As our ideas of allopathy (other-caused illness) have evolved so have our efforts to prevent contagion: public and personal hygiene, quarantine, isolation, sterile technique, antisepsis, inoculation, etc. But it was the emergence of the scourges of HIV and AIDS that underlies the mannerisms and rituals that we display nowadays to protect one another from each other's pathogens. The result is costly, both economically and environmentally.

Sidestepping the politically loaded notion that our fears and needs have been opportunities for industries to emerge and thrive in previously unpredictable arenas, let us briefly (informally, non-exhaustively) list the burdens of our not unfounded, but perhaps inflated, fear of contagion. (For brevity, I address only the hazard of infection.) These can be broken down into *economic costs*, both individual and public, and *environmental costs* (think green) of the various defensive measures we have adopted, expecting in turn provision of *individual protection* or *universal protection* – sometimes both equally, sometimes more of one than the other, and certainly not thoroughly all of the time. (Purists would be correct pointing out that widespread individual protection ushers in universal protection.)

Our contemporary/Western approaches to the potential of infection are associated with increased costs (materials and labour) that are passed down to us in the overall cost of healthcare and increased environmental effluent.

- So many individuals in any sort of function that entails frequent contact with the public (e.g. grocery store clerks) unnecessarily and in a copycat manner have taken to using disposable gloves and changing them frequently, even when not required to do so in their work.
- The increased use of gloves has increased the incidence of latex allergies – giving rise to a new industry to produce and market latex-free gloves.
  - Disposable gloves then require disposal as waste.
- Sightings of the use of facemasks by the public are increasing. Often this usage is unnecessary

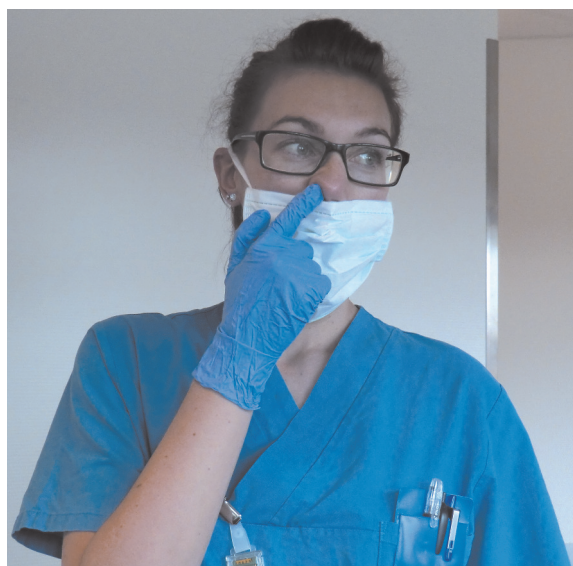
and an affectation that reflects extremist reactions to theoretic hazard.

- Facemasks eventually require disposal.
- Paper towels are being used to grab handles of WC doors from inside before exiting – which means trees must be cut to produce the paper towels, which become trash.
- The disinfectants and hand cleansers used institutionally, and now increasingly by individuals, contain chemicals, which cannot but enter the environment with as-yet-unknown effects.
  - Not unrelated to such practices is the imminence of pathogens resistant to the compounds, or of human allergies to the chemicals.
- There are, also, the costs of (a) determining the magnitude of a particular infective threat, (b) drawing up policy to deal with it, and (c) implementing preventive measures – not the least through educational programmes.

The list could go on, and the collateral burdens of others of our evolving safety-seeking habits could be treated similarly.

George Monbiot (published frequently in *The Guardian Weekly*) often writes on population growth, environment, the environmental consequences of our increasingly materialist and consumerist habits, and related topics, and he concludes that to help save the environment (and ourselves) we must change our habits and expectations. But he is realistic and alludes (mainly alludes) to the futility of such well-intentioned and hopeful prescriptions.

Despite time spent in training, our nurses were (they likely still are) unaware that they had turned scientifically reasonable prescription into mindless ritual. With contagion in mind, a similar judgement could be made about airport security procedures: (a) Take-off your shoes! And never mind that in passing you'll pick up some germs off the floors of airports. (b) Have the contents of your carryon luggage hand examined by an inspector who, between penetrating inside one valise and the next one, does not change gloves (not voluntarily, at least).



Given the human element lurking inexorably in the background, that the incidence of infections is not higher speaks not for the efficiency and efficacy of safety procedures, but more reassuringly for the resilience of the human body and its inherent, though not inexhaustible or infrangible, capacity to fight off pathogens. Yet ironically, it is also the human element that prevents a definitive dismissal of the notion that prescribed, but often ritualized, safety measures may at the end be futile, because our professional and personal lives, increasingly complex and demanding, influence our focus and dedication. We are increasingly overloaded (and distracted) with information that stoke fears, by regulations, by prescribed formal procedures, by personal needs or desires for pleasures. We are burdened by time limits and expectations of optimal productivity.

Without safety policies and procedures we would be worse off. But we should not be deluded into believing that they can or will fully allay our fears, ever. At the end, when we consider safety, we must ask not only what safety is and how to achieve it, but also the following: Ah, Safety, whither goes thou? At what cost? Is your safety net safe?

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## Author information

Jack Aslanian is a graduate of Carleton College and The University of Chicago Pritzker School of Medicine. He has divided time between decreasing amounts of clinical practice and increasing amounts of writing and medical editing. His English translations of the poetry of Paruir Sevak were published in Armenia in January 2011.

# Crowdpower in the era of 'health 2.0'

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## Abstract

Members of the social web are increasingly banding together and using web 2.0 technologies to actively participate in their own healthcare ('health 2.0'). This article gives an overview of how 'crowdpower' is impacting the field of healthcare, above and beyond merely offering emotional or informational support. It describes how the face of healthcare research is changing due to the technology-mediated collaboration between companies and ordinary patients, and how disease may be prevented with the help of the social web. Issues of health literacy and the role computer gamers are playing in the quest for new therapies are also discussed.

**Keywords:** Crowdsourcing, Healthcare, Health 2.0, Social health networks, Medical communications, Medical writing

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The social web has led to a democratization and acceleration of communication, since information can be exchanged globally and in real time between people from all walks of life. Increasing numbers of people are now using web 2.0 technologies to actively participate in their own healthcare ('health 2.0') in ways that would have been unheard of a few years ago. Members of the social web are harnessing their creativity and launching collective endeavours that will permanently change the face of healthcare. This power of the crowd extends beyond offering emotional support or exchanging information, for example between patients suffering from the same condition. It is equally involved in addressing health literacy issues, promoting research activities, preventing diseases, and even in the quest for new therapies.

## Offering emotional and informational support

For patients suffering from rare or chronic conditions, connecting with one another via disease-specific networks can be an invaluable source of

emotional and informational support. A study has shown that almost one in four (23%) Internet users living with high blood pressure, diabetes, heart or lung conditions, cancer or other chronic illnesses go online to find other patients with similar health concerns.<sup>1</sup> There are numerous high-quality blogs by patient experts and/or advocates that all offer a wealth of information: DiabetesMine is a site set up by a woman suffering from type-1 diabetes who shares medical information and practical advice on dealing with the disease.<sup>2</sup> Crohnology is a social health network for people with Crohn's disease and colitis to learn what treatments work, to meet other patients near them, and to track and share their health.<sup>3</sup> The site 'stupidcancer.com' was launched by a young man struck with a rare form of paediatric brain cancer who found himself isolated between the worlds of adult and paediatric oncology. A recent mother with a rare heart condition called spontaneous coronary artery dissection proactively started her own online community, which eventually led the Mayo Clinic to initiate research into the disease.<sup>4</sup>

## Addressing issues of health literacy

Crowdpower is also addressing issues of health literacy, or the ability to understand medical or health-related information, in new ways: a German website called 'What'sWrongWithMe', staffed entirely with a group of volunteer medical doctors, translates medical jargon into terms that laypeople can understand.<sup>5</sup> Although almost 600 specialists are helping to support the site, the demand for this service far outstrips its capacity, highlighting the unbroken need for clear communication to help patients understand their illnesses and make informed decisions about their health. A study from the United States has shown that one in two people only have intermediate skills when it comes to health literacy.<sup>6</sup> Barriers to understanding include not just difficulties in comprehending specialized medical terminology, but a

limited understanding of math, difficulty in taking in large amounts of information at once, and high levels of emotion and apprehension when dealing with illness in oneself or in a loved one.<sup>7</sup> This continues to be an area in which professional medical writers and/or communicators can make a valuable contribution by processing and presenting medical information in a manner that not just experts, but laypeople can easily understand.

### Crowdsourcing healthcare research

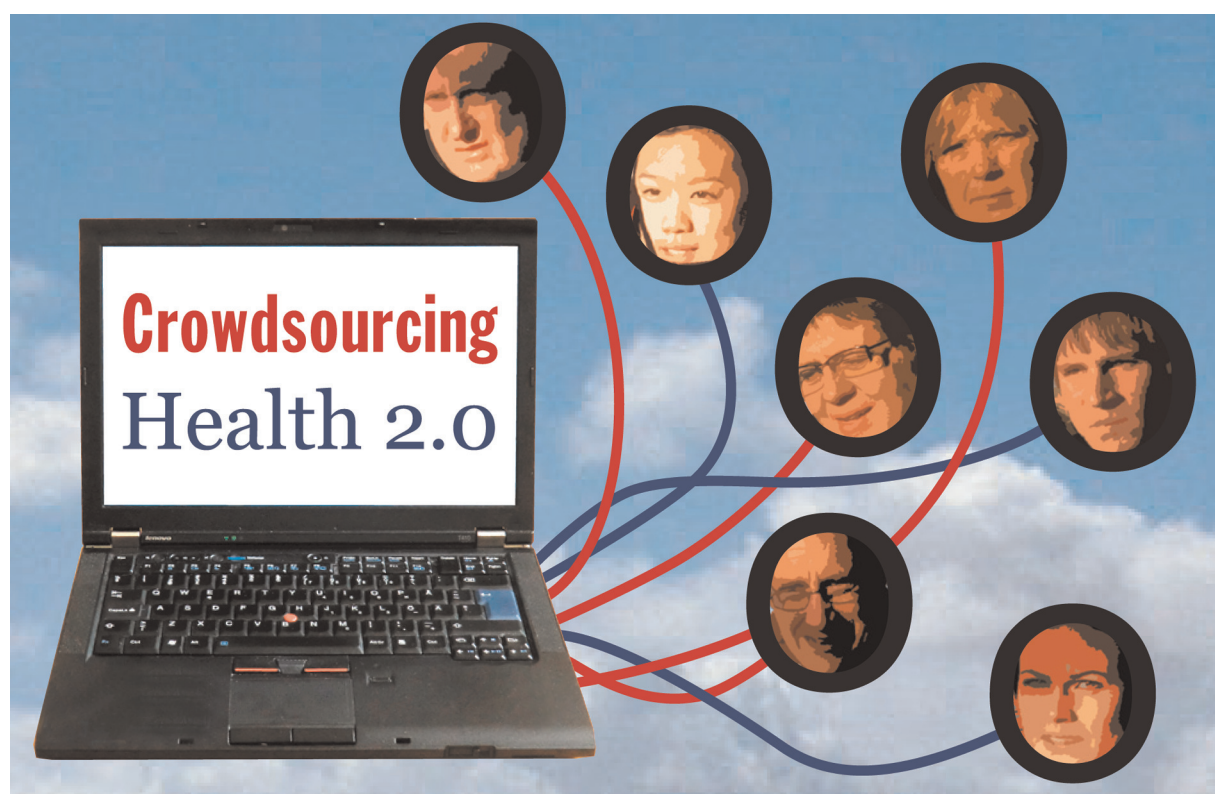
The advent of the social web has led to so-called crowdsourcing, i.e. using web-based technology to recruit large numbers of project participants. In the context of healthcare, crowdsourcing opens up new avenues of patient recruitment for clinical research trials and is a welcome development in the face of notorious difficulties many fields of medical research encounter.<sup>8</sup> Cancer is one area where finding patients can be especially challenging,<sup>9</sup> so the ‘army of women<sup>®</sup>’ is using the Internet to look for women from all around the world interested in taking part in studies on the cause and prevention of breast cancer.<sup>10</sup> What is new is that recruiting is no longer limited to researchers or institutions. In the spirit of ‘citizen science’, patients motivated by their own health issues are now able to bring their own ideas

into play and initiate trials with the help of web-based platforms.

### Organizing research into rare diseases

Two leading players in researcher-organized, crowd-sourced health research studies are PatientsLikeMe<sup>11</sup> and 23andMe.<sup>12</sup> PatientsLikeMe offers patients an online platform where they can share their health data and participate in clinical trials. The company generates revenue by anonymizing the data collected and selling it to relevant life science and health management companies. In one widely published example, data collected from a cohort of 150 amyotrophic lateral sclerosis (ALS) patients recruited through PatientsLikeMe succeeded in refuting the results of a previous study with a significantly smaller patient cohort on the effects of lithium carbonate on ALS progression.<sup>13,14</sup>

23andMe is a for-profit company whose business model is based on genome testing for private customers, combined with a web-based social network that allows people to ‘participate in research while exploring your own genetics’. Among others, they have research communities on Parkinson’s disease, sarcomas, and myeloproliferative neoplasms that people are free to join, and have published data on the correlation of self-reported medical data with known genetic associations.<sup>15</sup>



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## Empowering patients to initiate their own studies

In contrast to purely researcher-organized studies, the web now also has platforms for crowdsourcing health research studies where any member (professional or layperson) can initiate a study. One example is DIYgenomics, a non-profit research organization that capitalizes on the fact that sinking costs in genomic sequencing are allowing people to obtain their own genomic data.<sup>16</sup> DIYgenomics is partnering with the start-up Genomera<sup>17</sup> to crowdsource genomic research into topics like vitamin deficiency, ageing, and mental performance. Participants share their genomic and phenotypic information via the website which then collects, analyses, and visualises the study data. The service is free of charge, but the company hopes to generate revenue through referrals, sponsors, and analytic services.

Althea Health<sup>18</sup> is a start-up that provides the infrastructure for people to plan studies via its website and then deploy them on smart-phones. As an initiator, you define the aim of the study and its key parameters (symptoms, observations, treatments etc.), post an enrolment form on the website and are subsequently responsible for recruiting participants. Collected data are aggregated and reported back by the company. Patient-oriented sites like CureTogether<sup>19</sup> and QuantifiedSelf<sup>20</sup> focus mainly on bringing together like-minded people interested in learning more about their health or certain conditions, other people’s experiences and better treatment options. Although experts agree that crowdsourced healthcare research can be a useful extension of traditional clinical trials,<sup>21</sup> the scientific rigor of these kinds of studies must be subjected to careful scrutiny before results are extrapolated to broader populations. The problem of self-report bias and sample sizes in particular are apt to be more relevant in crowdsourced contexts.

## Preventing diseases before they spread

People who are knowledgeable about their risk factors and predispositions for certain diseases can be motivated to improve their own outlook. The health 2.0 environment is facilitating access to tailored programs for specific diseases, as in the case of Omada Health, an online start-up focusing on disease prevention.<sup>22</sup> Their first web-based program is concentrating on people with prediabetes, i.e. those with blood glucose levels sufficiently high to indicate that they may develop type-2 diabetes. People are divided into small groups and matched with an Omada coach

who guides patients through a 16-week lifestyle course. The aim is to combine the advantages of technology with social support to enhance adherence and thus improve participants’ long-term health outlook.

In the field of pandemic tracking and prevention, search engines can be used to monitor global disease activity,<sup>23</sup> as with Google’s Flu Trends,<sup>24</sup> a development which has even caught the interest of international regulatory and control authorities. In a study done during the 2007 H1N1 pandemic in Europe, it was shown that there was a good correlation between the numeric estimates of sentinel physicians and Google’s Flu Trends reports.<sup>25</sup> The European Centre for Disease Prevention and Control (ECDC) thereupon ranked Google’s Flu Trends as a useful supplementary tool to monitor pandemics.<sup>26</sup>

## Finding new therapies with gamers’ help

The power of the crowd also comes into play in a field more commonly associated with frivolous nerds than with healthcare – computer games. The online science game FoldIt capitalizes on humans’ superiority over computers in solving three-dimensional problems by asking participants to help fold proteins.<sup>27</sup> Gamers have successfully improved enzymes and discovered new strategies and algorithms at their computers which may potentially help scientists find new treatment options for certain diseases.<sup>28,29</sup>

## Conclusion

The social web has spawned a myriad of healthcare-related communities that are exchanging information and getting actively involved in their own health issues. A characteristic of this trend is the blurring of the boundaries between ‘experts’ and ‘laypeople’. Thanks to internet technology, not just medical professionals, but engaged ‘citizen scientists’ can also play a key role in moving science forward. In the world of health 2.0, the power of the crowd is subtly changing many areas of healthcare – from clinical research to disease prevention to the search for effective treatments.

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## Author information

**Ursula Schoenberg** is a bilingual German-American medical writer. She offers professional copywriting, editing, and translation to companies, communications agencies, and organizations seeking to strengthen their messages in a global market. One of her fields of interest is how new channels of communication are changing the healthcare landscape.



# Networking effectively: *Essential* for being successful in business

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## Abstract

One of the keys to being successful in business is the ability to network effectively. Making efficient use of the interactive communication tools available to you today, such as business networking websites like LinkedIn, Plaxo, and Xing and microblogging platforms like Twitter®, not only increases your chances of winning new clients and business but also helps in retaining them. This article describes the steps to efficiently win and retain clients and how to use business and social networking platforms to increase your chances of success.

**Keywords:** Business, Social networking, LinkedIn, Twitter®, Communication

The age-old adage 'it's who you know and not necessarily what you know' is very true in business. But getting to know the 'who', particularly when you're trying to operate internationally, can be tricky, especially in this day and age where sending emails is not always enough.

## Market yourself to develop business

Gaining contacts and future business associates is one of the most important practices in any business. Having a product or service to sell with no buyers is destined to end badly! Many people underestimate the power of sales. Coming from a sales background, I believe it is key to sell yourself and services (or product) properly. Simply being an exceptional writer is not enough. Sitting in your office, you can't just expect to receive work because you have X years of experience in the industry and have a website. You need to market yourself appropriately and make the buyer want to buy your services in the near future.

## Your role as a businessperson

If you are seeking new clients, remember that you are not only a writer but also a businessperson, which requires a change in philosophy and modus

operandi. Yes, you're a great writer, have X years of experience and have written an array of documents in a dozen medical fields, but can you bring the business in to showcase your talents? Are you winning business the right way? More importantly, are you retaining your business? Even if you work for a company, you need to make new contacts to ensure a steady flow of work.

This is where business relationships become paramount. Without any sort of relationship in life, be it with family, friends, colleagues, or even your personal trainer at your gym, your situation won't work nor will it evolve. You must build relationships and gain trust through exceptional work, but you also must remember to add the human element too. Business is business, but people buy people.

## Building relationships with business network websites

We are in an age where modern technology has transformed our way of life and business, simplifying and speeding up almost everything. Building relationships has also been made easier; are you on Facebook® with your family and friends? Do you stay up to date with loved ones over social media, seldom sending emails? Well, this approach also applies to business life, if you use it wisely.

The biggest business networking website is LinkedIn ([www.linkedin.com](http://www.linkedin.com); Figure 1). Others such as Xing ([www.xing.com](http://www.xing.com); Figure 2) and Plaxo ([www.plaxo.com](http://www.plaxo.com)) also have a following in Germany and America, respectively, but LinkedIn is number one. Almost everyone in business is on it, and if they're not, then it would be a very good idea if they were because, increasingly, employers and business partners want to see a professional online presence. Your online persona and CV play a big part in modern business, especially in medical writing, where your profile, when completed, serves as a showcase of your experience and achievements.

The screenshot displays a LinkedIn profile for Bilal Bham. The profile includes a header with the name and title, a profile picture, and a status update. The main section lists current and past employment, education, and connections. On the right, there are promotional banners for profile completion and ads for software and eBooks. A 'Who's Viewed Your Profile?' section at the bottom right shows recent profile views and search appearances.

LinkedIn has helped me to win a lot of business and keep in touch with all my clients and many other professionals and friends

Figure 1: My LinkedIn profile page.

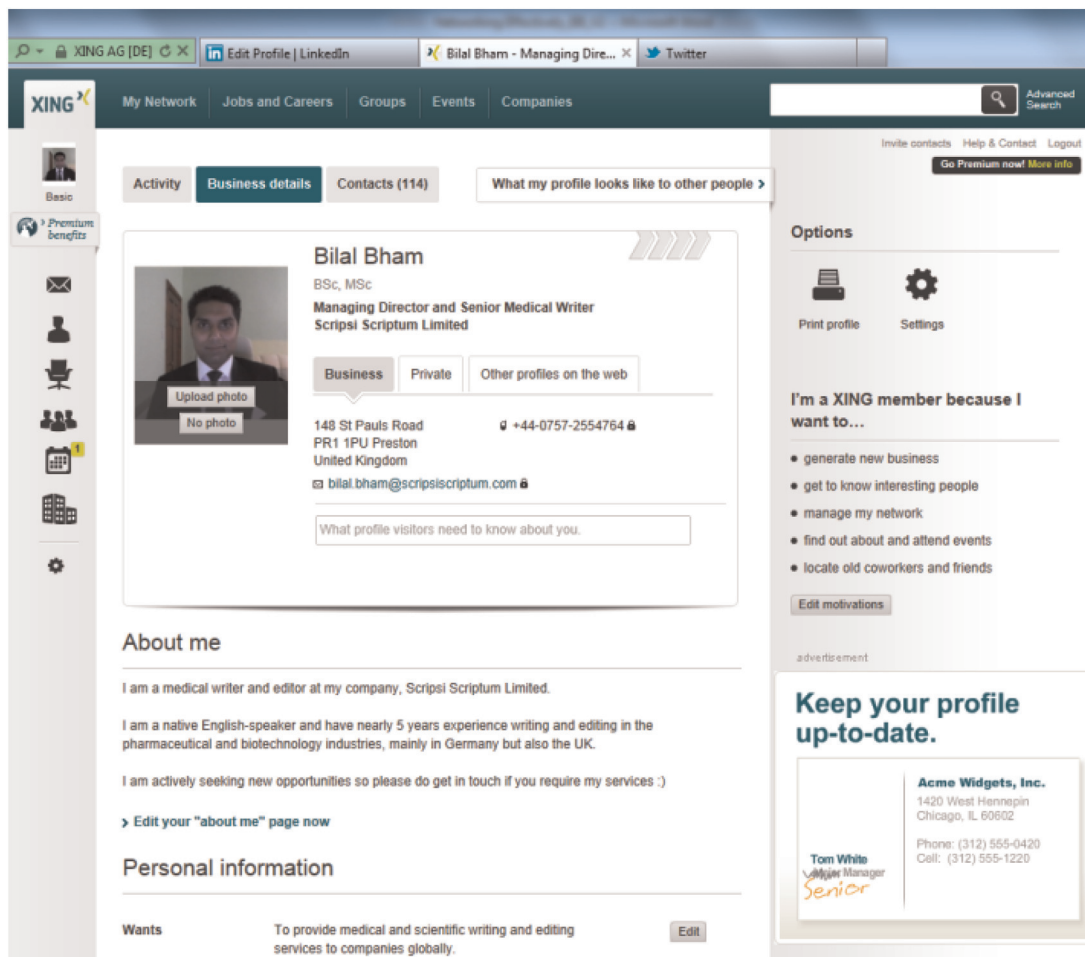
## LinkedIn and Xing – What are they?

LinkedIn is a business networking platform, like a Facebook® for professionals, which allows you to connect with people in the professional world. You can either be invited to it or go to the website yourself and create a profile. There are different levels of membership, ranging from the relatively limited but free standard membership to different levels of premium membership, which requires a paid subscription but opens up many features like sending messages to people who aren't connected to you and seeing more details in their profiles. The more people you are connected to and the more groups you subscribe to, the more people will be available to see what you have to offer. Xing is similar to

LinkedIn, in that you can be invited or join up yourself, and premium membership makes available a range of features unavailable under basic membership such as writing to people you aren't connected to.

## How to make a new business contact

Blindly phoning companies, so-called 'cold-calling', is only productive to a certain degree – you usually end up being given the generic info@ email address. Therefore, you need to have a focus; simply asking for a 'medical writing manager', for example, won't help and you are unlikely to get any further than the gatekeeper. Having an objective in mind and not losing focus is very important – be single



Xing has allowed me to retain contact with my German colleagues and friends

Figure 2: My Xing profile page.

mindful when doing business development. Use the following approach to make a new business contact: research, identify, call, present, connect and retain.

#### *Research*

Do some background research on a company that could be a potential client. You might decide that certain pharma or biotech companies, CROs, or medical communications companies look interesting because they have had a good measure of recent success with drug trials or acquiring new business. Frequently visiting pharma news websites such as [www.worldpharmanews.com](http://www.worldpharmanews.com) and other similar websites will help give you an insight into the industry and will allow you to act upon breaking news so that you can be more focused in chasing potential business leads.

#### *Identify*

Use LinkedIn, for example, to search for individuals relevant to your field working within that company.

Typically, these are regulatory affairs managers, publications managers, medical writing managers and, if need be, the boss of the company.

#### *Call*

This is where your writing abilities take the back seat and your abilities as a business person, in this case your sales skills, take precedence. Phone the company and ask to speak to the person in question directly. You may encounter someone blocking your progression to the person you want to contact – a so-called ‘gatekeeper’ – but this is where your personality and presence of mind and a bit of guile, kick in.

#### *Present*

Once through to the decision-maker, show your personality and present yourself in the way you see fit. What works for one person won't necessarily work for another, but the one piece of pertinent advice I can offer is to keep your

conversation short and succinct. Insist on sending over a summary of your experience and a copy of your CV for their records.

### Connect

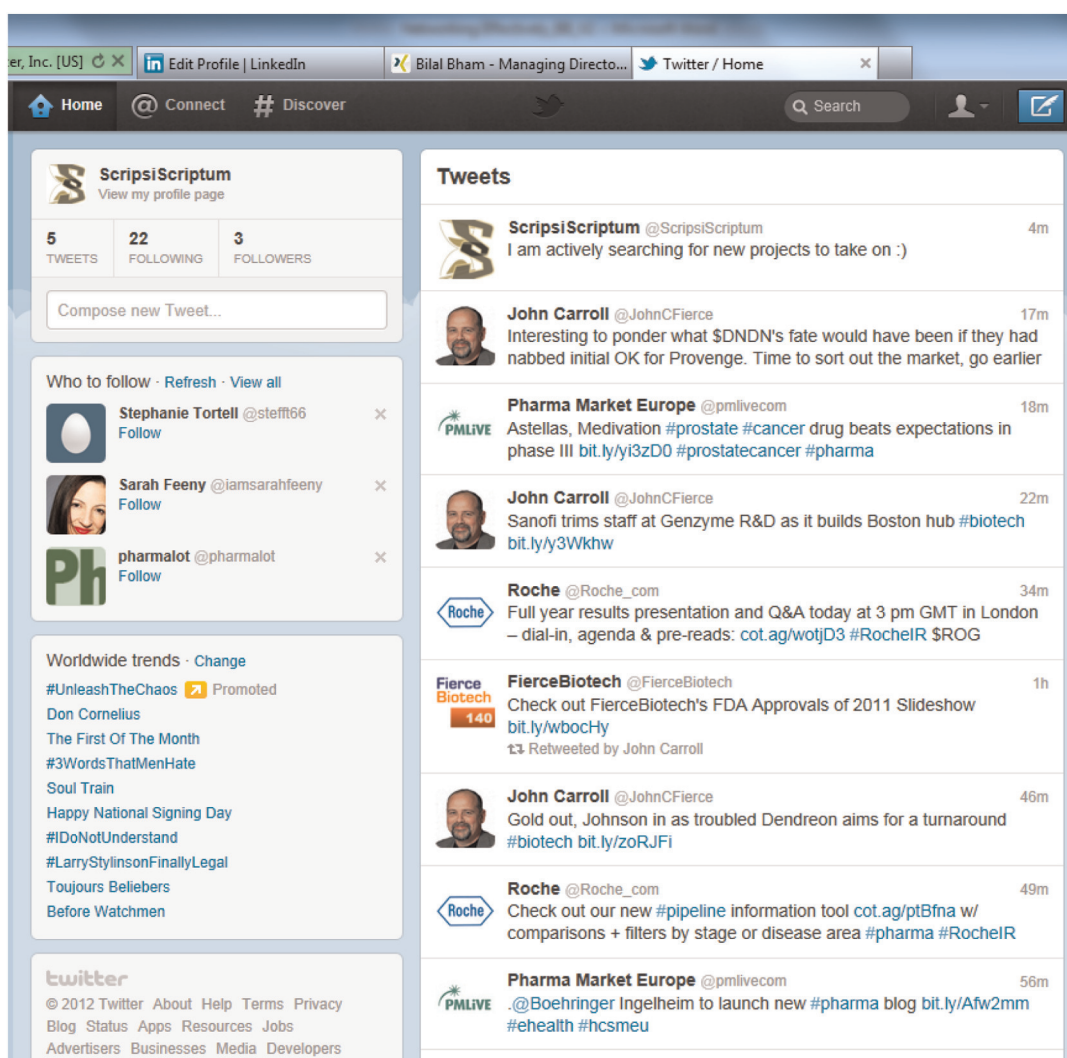
Insist on trying to connect with the person you have spoken to over LinkedIn and/or Xing so that they have access to your profile page at the click of mouse.

### Retain

After connecting, try staying in contact without becoming overbearing, perhaps sending updates on your experience or any changes, or even simple courtesy messages so that you keep their attention and they don't forget who you are!

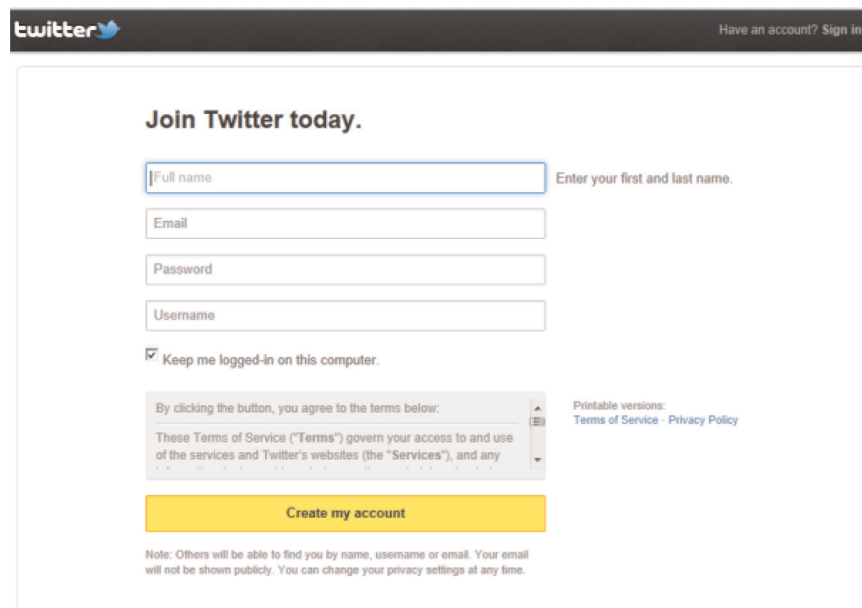
## Tapping into social media

Keeping the attention of clients and potential clients via platforms such as Twitter® (www.twitter.com; Figure 3, Figure 4 and Box 1) in addition to LinkedIn is also rewarding. Twitter® is a free and non-profit social networking and microblogging platform where people can send out short messages via status updates, so-called 'Tweets'. You can 'follow' or be 'followed' by people on Twitter®, whoever they are, meaning that you can view their Tweets on your profile and vice versa. You can also view Tweets from people you are not following and vice versa. It works purely because of the users, who may be ordinary individuals like you and me, famous people, companies, or institutions and so forth who will send out Tweets about what they are doing, what is coming up or any breaking news or gossip, which then spreads through reblogging.



Twitter has given me the opportunity to follow and be followed by professionals in the pharmaceutical industry via microblogging

Figure 3: My Twitter® profile page.



How to create a Twitter account

Figure 4: Joining Twitter®.

**Box 1: Twitter®: the basics**

Website: [www.twitter.com](http://www.twitter.com)

Profile: microblogging social networking platform limited to 140 characters per status update, i.e. 'Tweet'

Accessibility: quick, simple, and easy to set up an account

How to create an account:

Creating a Twitter® account is the simplest account you will ever create! (Figure 4)

Go to [www.twitter.com](http://www.twitter.com), fill in your name, your email address and think of a password, then click on sign-up, which will allow you to create a username, and voila, you are finished! It really is that easy and the rest of your profile is simple to complete because the registration process is quick and takes you through it, it is very user-friendly!

For further information: <https://support.twitter.com/>

Some basics: The @ and # symbols:

The # symbol, called a hashtag, is used to mark keywords or topics in a Tweet and is used as a way to categorize messages.

An @reply is any update posted by clicking the 'Reply' button on another Tweet.

Connectivity: You can 'follow' or be 'followed' by people on Twitter®, whoever they are, meaning that you can view their Tweets on your profile and vice versa. You can also view Tweets from people you are not following and vice versa.

Mobility:

Using Twitter® via your smartphone is also very easy. To use it via your smartphone, either visit the website or even better, download the free app, put in your details and away you go!

Twitter® is very simple. Unlike Facebook®, where you have many fields to complete on your profile and have an unlimited number of characters for your status updates, Twitter® is the converse. The amount of information you can put in your profile is limited – tweets are restricted to 140 characters. Sending out informative or often simple tweets to your followers (who may be your clients) keeps you

alive in their minds, meaning that they're less likely to forget you. Being connected over Twitter® is also increasingly seen as the new way of forming and developing business relationships as well as spreading breaking news. One of the most convenient features of LinkedIn and Twitter® is that they can be linked, so that updating your status on one of the platforms will automatically do the same on the other.

## **Don't forget to live in the 'real world' – face-to-face networking still works!**

Remember that you don't simply want to become a voice over the phone or a still photo online. Networking events, conferences, congresses and so forth are equally vitally important. For example, I connected with someone over LinkedIn, but they never replied to any of my follow-up emails; however, upon meeting them in person, I swiftly got a reply with a view to potential future business. So, attend events, and never leave your business cards at home! Again, ask to connect with them over LinkedIn. It is them you want the business from and to connect with, so you must be proactive in your efforts to connect with them. Don't simply expect them to connect with you – they're likely to be busier than you are and you won't be the only person who will have given them your business

card. Stand out in some way and try to leave an impression!

## **Summary**

Networking effectively for the benefit of your business is important in today's highly competitive business world. Building and maintaining long-term relationships are key to successful and mutually beneficial business relationships. Current business and social networking platforms such as LinkedIn, Xing, Plaxo, and Twitter<sup>®</sup> have simplified interactivity by tapping into our innate needs to communicate. Communicating face-to-face and via the telephone will never be replaced, nor should they be, but taking full advantage of the interactive business and social networking tools available is an intelligent investment of time and effort that will help make your business development a bit easier and more efficient.

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## **Author information**

**Bilal Bham** has a BSc honours degree in Genetics from the University of Manchester, which included an industrial placement year at European Molecular Biology Laboratory (EMBL) and the European Molecular Biology Organization (EMBO) in Heidelberg, Germany. He also completed an MSc in Immunology and Immunogenetics at the same university.

# The moving image and your business

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## Abstract

Using online video to promote business is widespread, but the skills required to make effective use of the medium are relatively rare. Dr Phil Moran discusses some basic ways to improve video production, ranging from advice on the technology through to the front of camera presentation. Future developments of online video are also discussed and Dr Moran asserts that the rules of story telling will still be effective.

**Keywords:** Video promotion, Video blog, Presenting, Personality, Audio production, 3D video

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## Article

There is a story about one of the Lumiere brothers' earliest public film screenings, in which the audience was seen to duck in fear when they watched a locomotive on the screen heading towards them. Although the story itself is probably an urban myth, people were amazed at the perceived realism of the projected image, and in 1895 were prepared to pay to watch 'documentary' films that were essentially just raw footage of everyday life. Five years later, the brothers were still producing many short movies each year, but the majority now had some kind of story, as people had outgrown the novelty of their cinématographe device.

Interestingly, the very invention of the moving image was for scientific purposes rather than public entertainment (see Figure 1), and this progression from spectacle to story can also be seen in modern technologies such as online video. Look up the first clip ever uploaded to YouTube™<sup>1</sup> and you'll find Jawed Karim, a co-founder of the website, in a zoo saying why he likes elephants. Today, the quality of some material that is produced and distributed solely through YouTube™ is comparable to prime time television – as are the audience numbers. Convergence of technology has arrived and now anyone can be a broadcaster, either with a recorded channel like YouTube™, or

even live broadcasting with a site like Ustream.<sup>2</sup> It's online for you to use for free, and all you need is a camcorder and a laptop to make your film. The problem is that the same is also true for everyone else, so how can you make the medium best work for you and your business, and push yourself ahead of the competition?

First, sound is more important than vision. Strange but true. If your audience can't hear you, it will frustrate them and they will switch off. If the visuals are bad, but they can hear what's going on, they are much more likely to stay with you. Think of films like *The Blair Witch Project* and *Paranormal Behaviour* and you'll see (or hear) that sound is what gives a film bite.

In practical terms this means getting your microphone as close to your source as possible. If you are video blogging using the webcam on your laptop, you might get away with using the inbuilt microphone, but if you're presenting to camera on a busy street, you need either a directional microphone or a lapel microphone. The lapel microphone goes on your lapel (duh!) and so is always close to your mouth, whereas the directional microphone needs to be pointed at your mouth without anything else behind. This usually means pointing upwards from below. Don't use the internal microphone on the camera, it picks up sound in all directions and is never close enough to the source of the sound you want people to hear – i.e. you.

Second, screen personality matters. Nearly, all television programmes have a presenter, and this is because broadcasters know that it's the best way to connect with an audience. If you are going to front your own video, be over the top about it. Gesticulate with your hands, be enthusiastic and speak louder than you do in normal conversation. You want to convey your enthusiasm, expertise, but also genuineness. It's a difficult balance, but practice makes perfect. Get honest opinions about your performance and if you can find someone who can do it better than you, use them. There's no shame in it – screen personality is a developed skill and takes time to learn.

Some great examples of effective use of online video are Maria Forleo<sup>3</sup> ([www.mariaforleo.com](http://www.mariaforleo.com)) and Adam Shaw<sup>4</sup> ([www.adamshaw.co](http://www.adamshaw.co)). Forleo clearly has money for production – lighting, studio, editing, etc., whereas Adam Shaw is simply using a camcorder. Both use the same techniques though; they speak with authority, smile a lot, and are always positive, giving you confidence in their message.

Third is story. Good audio and on-screen personality will grab your audience's attention, but then you want to keep them watching. Story doesn't only apply to cinematic films and television drama; it can be useful for any film.

Have you ever received those spam e-mails with a link to a website where there is a guy telling you about all the get rich quick schemes that he has tried over the years or all the muscle-building supplements. What are these people selling? Get rich quick schemes and muscle building supplements! The reason they don't say what they're selling at the start is because they want to draw you in with a story – their story.

So what is 'story'? Well that's too big a topic for this article, so let's just concentrate on the main process; building up an expectation in your audience, making them wait, and then rewarding them (or punishing them) at the end. It sounds rather academic, so let's illustrate with a couple of examples:-

Imagine you're a pharmaceutical company who makes a new drug to combat asthma. Do you start with an announcement of the new drug? No, you start with a child coughing and wheezing, trying to catch their breath. Put it to a voice over that says 'When Jamal was a child, playtime meant watching his friends run around outside in the Sun whilst he put on his ventilator'. Voila, we have set up our story – a character that the audience empathizes with and a situation that they want to be resolved. Our voice over can then talk about the company making the drug, and in the end we can reward our audience by showing Jamal playing in the sun with other kids.

Sounds like advertising, doesn't it? That's because it is! Exactly the same principles apply; we need to think about benefits, not features.

How about you being offered sponsorship to make a regular video blog reviewing the latest hospital equipment coming onto the market? The more viewers you get, the more you'll be paid. Do

you simply sit in front of your screen and explain the specifications of the latest hi-res magnetic resonance imaging equipment? No, you announce it and ask the question 'How good is it? I visited Great Ormond Street hospital to have my own brained scanned' – followed by a mini on-location report. Again, you're setting up an expectation by asking the question, but making your audience wait for the answer till the end of your report – it's a story.

As with any story, the more interesting, shocking, engaging, or funny your material is the more likely your audience will keep watching.

How about you want to set up a website using video to sell people a get rich quick scheme ... oh hang on, we've already done that one.

A great example of the use of story in online video is 'Will it Blend'?<sup>5</sup> Blendtec, a blender manufacturer started demonstrating how good their equipment was with a regular show on YouTube™ in which they blended a different item each week – iPhones, Barbie dolls, silly putty. You name it, they blend it. The very title of it sets up the expectation – and of course you are always rewarded at the end.

So what about the future? What's the next technology that we'll all want to play with? It's always difficult to predict, but there are signs that 3D will become mainstream. It already is in the cinema, and YouTube™ recently launched a 3D channel.<sup>6</sup> Consumer electronics such as 3D video cameras are widely available and you can even get laptops and cell phones for viewing 3D material that work without glasses – incredible.

For myself, I've made a few 3D films for the corporate world and I have noticed that we are now transitioning from spectacle to story. Most of my early jobs were only of footage – the clients simply wanted to show something new. But now the requests are also for 3D with voice over and story – 3D alone is losing its wow factor.

Whatever way the technology goes, I'm certain that the three principles I have discussed here will still hold; get good sound, use a good on-screen personality, and above all, tell a story.

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4. [www.adamshaw.co](http://www.adamshaw.co)
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6. [www.youtube.com/user/3D](http://www.youtube.com/user/3D)



### The first motion picture

The first motion picture was a scientific experiment conducted by Eadweard Muybridge in 1878. If you happened to have searched Google on 9th April you might have noticed that the banner on the search engine were a series of silhouettes of a horse galloping as a birthday greeting to Eadweard Muybridge. Had he lived that long, he would have been 182 years old. He made the 'film' to resolve a debate about whether all four hooves of a horse are off the ground at once when it gallops. A series of cameras were set up in a line, each of which took a photo as the horse galloped past. The images were then copied onto a disc and viewed through a 'Zoopraxiscope'. Thus Muybridge proved that indeed there is a point when all the hooves are off the ground. The experiment was commissioned by a race-horse owner in 1872 but was interrupted while Muybridge faced a charge for murdering his wife's lover with a shot gun. He was acquitted for 'justifiable homicide'. After this episode he put his son into an orphanage believing his wife's lover to be the father, which is unlikely as the son looked very much like Muybridge. While Muybridge became famous with his motion pictures lecturing to audiences at the Royal Institution in London, his son became a gardener and ranch hand.

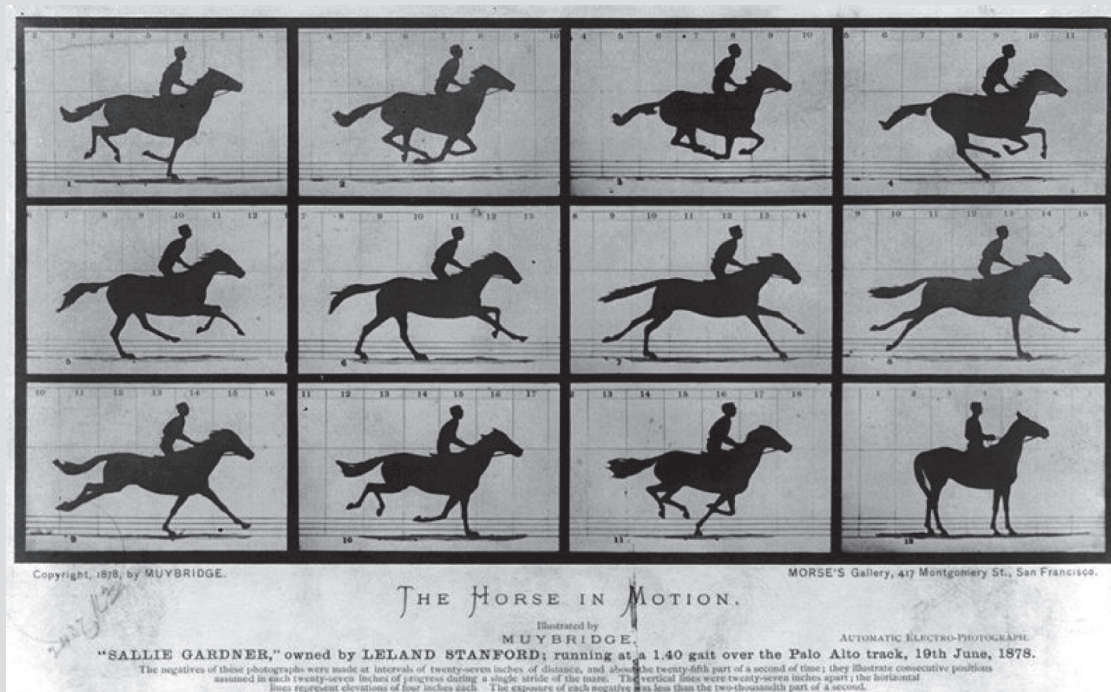


Figure 1: This image is reproduced from [http://en.wikipedia.org/wiki/File:The\\_Horse\\_in\\_Motion.jpg](http://en.wikipedia.org/wiki/File:The_Horse_in_Motion.jpg). Under the Wikimedia Commons licence.

### Author information

Dr Phil Moran is a former physicist who became a film-maker in 1999. His work ranges from television documentaries to cinematic features and he acts as a consultant for several international corporations on their use of video. His company FFAB ([www.ffab.co.uk](http://www.ffab.co.uk)) works throughout Europe and the company recently launched new services in New York.

# Forgive me for repeating myself: Self-plagiarism in the medical literature

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## Abstract

While plagiarism of others' work is universally condemned, authors' reuse of their own words and data (so-called 'self-plagiarism') is a far more contentious issue. The recycling of one's own text, in particular, polarizes opinion: some consider it unacceptable, whereas others don't see anything wrong with it at all. This being so, it is unsurprising that there are no widely adopted guidelines outlining which (if any) and how much text may be recycled. My aim in writing this article is to briefly introduce the different types of self-plagiarism; to present the views of journal editors and other interested parties and describe ways in which the former are combating abuses; and to highlight some of the steps authors can take to avoid trouble.

**Keywords:** Plagiarism, Self-plagiarism, Text recycling, Data recycling

While tales of students and researchers passing off others' words as their own are commonplace, the issue of scientists plagiarising their own work hasn't created anything like the same hoo-ha. Indeed, some question whether there's anything wrong with it at all.

'Self-plagiarism' means different things to different people. While to some it is the republication of one's published data in a modified or unmodified form (so-called 'data recycling'), others would include the reuse of one's old text ('text recycling') in their definition.

An editorial in *The Lancet* from 2009<sup>1</sup> makes a clear distinction between data recycling and text recycling, referring to the former as 'unacceptable' and the latter as 'less of a crime'. However, responding in the same journal, Iain Chalmers<sup>2</sup> of James Lind Library, Oxford rejected the idea that reuse of one's own words is necessarily a bad thing, claiming

that getting an important message across outweighs the interests of editors and publishers.

Others seem to share this view. In a 2001 survey of 195 health education staff at US universities, nearly two-thirds of respondents were of the opinion that inclusion of the same section of text in multiple articles was acceptable.<sup>3</sup>

## Unacceptable practices

In a recent editorial, the editorial board of *ACS Nano* describe data recycling in strong terms – 'fraud', no less.<sup>4</sup> The authors rail against the waste of peer reviewers' time, warn of the loss of reputation and likelihood of getting caught, and lay the blame squarely on pressure on academics to publish.

The *Lancet* editorial identifies deception as the central issue here. The authors of the *ACS Nano* article concur, opining that it 'comes down to the central issue of deception – were the authors trying to deceive the editors, the referees, and the readers [by] presenting recycled data, text, and figures as entirely new material'?

The consequences of deliberate attempts to mislead by recycling data or large amounts of text can be serious – retraction, submission bans, getting grassed up to one's more senior colleagues – and rightly so.

## Text recycling

The reuse of one's own words is a far greyer area. When an author replicates descriptions of methods or other text from similar studies, it is perhaps because (s)he does not consider rephrasing to be a worthwhile exercise. Why waste time rewording perfectly written text merely to avoid the charge of self-plagiarism?

Stuart White<sup>5</sup> wonders as much in a letter of apology to *Anaesthesia*, written after he got into a bit of bother for publishing related (but different) articles with the same title in different journals.



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He goes on to bemoan the lack of guidance for authors in his position, and argues that it is up to journal editors to decide what constitutes self-plagiarism.

But couldn't they use some guidelines too?

While the International Committee of Medical Journal Editors (ICMJE) guidelines<sup>6</sup> touch on specific topics (such as the publication of important medical guidelines in multiple journals in order to reach a wider audience), they do not address all forms of self-plagiarism. A far more useful resource is Miguel Roig's guide to ethical writing<sup>7</sup>, essential reading for anyone concerned about any aspect of plagiarism. Roig defines what he considers to be the major types of self-plagiarism (see Table 1),

Table 1: Forms of self-plagiarism

Data augmentation*	Publication of old data with new supporting data as a new study
Duplicate publication*	Submission of essentially the same article for publication in two different journals
Redundant publication*	Publication of previously published data (with or without new data) with a new angle or focus
Salami slicing	Publication of different results from a study as separate papers when they would best be presented together**
Text recycling	Reuse of published text in a new publication

Adapted from<sup>7</sup>

\*Data augmentation, duplicate publication, and redundant publication are all forms of data recycling.

\*\*It is generally assumed that the motivation for this practice is to maximize the number of publications obtained from a single study.

explains why they are a problem, and provides helpful advice on maintaining high ethical standards.

Nonetheless, the apparent lack of official guidelines covering text recycling makes it hard for authors, editors, and readers alike to judge what is acceptable.

### Staying out of trouble

Copyright is an obvious practical issue to consider. The authors of an accepted manuscript are often required to sign over copyright to the publisher. Subsequent reproduction of parts of the manuscript may constitute a breach of copyright. (Different publishers have different rules governing the amount of text that may be reused without permission.) A number of journals do, however, allow authors to retain copyright, and the 'fair use' clause – which permits limited reproduction of one's own work for specific purposes – affords some room for manoeuvre.

One way to avoid self-plagiarism in methods sections is to describe the procedures briefly and provide references to previous articles in which they are described in full. However, this is not an entirely satisfactory solution as it risks inconveniencing the reader (who may be forced to refer back to, and perhaps purchase, these previous articles).

Some consider methods to be a special case. *Anesthesia & Analgesia*<sup>8</sup>, for example, permits verbatim copying of descriptions of methods, but not other text, by the original author. Other journals, however, do not. In short, there is no consensus.

The ACS *Nano* article quotes the ethical guidelines of the American Chemical Society,<sup>9</sup> according to which appropriate citation and use of quotation marks is necessary and sufficient to legitimize text recycling. However, convention dictates that it is not okay to present a whole page of methods in quotation marks. Roig, meanwhile, advocates the '[use] of quotations and proper paraphrasing'.

### A declining problem?

Plagiarism in general has never been easier to detect. A range of detection software is now available including eTBLAST, a free tool available from the Virginia Bioinformatics Institute website,<sup>10</sup> and journals and publishers are waking up to the benefits of these new resources.<sup>11(1)</sup> *Anaesthesia*, for example, now uses proprietary software to analyse every submitted article for evidence of plagiarism.<sup>12(2)</sup> (Describing this new practice in 2010, Editor-in-Chief Steve Yentis reported that his journal had directly rejected 4% of submitted articles because of

plagiarism in the year since it was introduced, but sadly failed to pinpoint the precise grounds on which decisions to reject are made.)

There are signs that efforts to tackle the duplication of manuscripts may be working. The number of new articles deposited in Déjà vu – an online database of Medline articles that are ‘highly similar’ to other Medline articles<sup>13</sup> – fell by approximately half in relative terms between 2006 and 2008.<sup>14</sup> Whether this change reflects better detection of self-plagiarism by journal editors or increased wariness on the part of potential offenders is open to speculation.

### How much is too much?

Not everyone would be overjoyed if I were to take a paper I had published and create a new one by merely replacing the data for one disease with those for another – as Andrzej Jendryczko more or less did in a notorious case that came to light in 1997.<sup>15,16</sup> But how much repeat text *is* okay?

In the absence of established guidelines, Drs Richard Kravitz and Mitchell Feldman of the University of California polled a number of experts for their opinions.<sup>17</sup> While many considered 10% an acceptable amount of recycled text, none felt that anything above 30% was reasonable. Similarly, ‘some editors’ have operated on the principle that ‘overlap of more than one-third of the material’ in review articles is too much, according to a World Association of Medical Editors (WAME) report from 2004.<sup>18</sup> Earlier sources quoted recycled text limits of 10<sup>19</sup> and 30%.<sup>20</sup>

Wherever one draws the line, consideration should perhaps be paid to the background of the author. For a non-native English-speaker who had difficulty describing something first time around, finding a second set of words to describe the very same thing may be an insurmountable challenge.

### Conclusion

Both authors and editors would benefit from a clear set of guidelines. The former would know how to avoid trouble; the latter would know when to take action and what action to take.

### Acknowledgement

My thanks to Miguel Roig for his helpful comments on an earlier version of this article and for directing me to some very useful information sources.

### Notes

(1) In researching this article, I tested whether two free Google search-based plagiarism detection tools – Article Checker (<http://www.articlechecker.com>) and Dupli Checker (<http://www.duplichecker.com>) – could recognize abstracts retrieved from PubMed. While Article Checker struggled to determine the origin of any of the abstracts I threw at it, Dupli Checker spotted signs of plagiarism in most cases, but produced different results when performing identical searches. A third plagiarism checker, available at <http://plagiarisma.net>, was far more effective (flagging almost every sentence of every abstract as unoriginal), but free use is limited to five searches per day.

(2) CrossCheck, available to members of academic publisher organization CrossRef. Users pay a per-document fee and an annual administration charge.

(3) In fact, the paper Jendryczko ripped off wasn’t even his; it had been written 12 years previously by fellow Pole Tatiana Gierek and her colleagues. Remarkably, Gierek herself appears to have borrowed excessively from her own work on occasion (<http://spore.vbi.vt.edu/dejavu/duplicate/67233>).

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Stephen Gilliver studied for a PhD in Cell Biology at the University of Manchester. After working as a postdoc at the same institution and an associate lecturer at Manchester Metropolitan University, he became a freelance copy editor. He is now the science editor at the Center for Primary Health Care Research in Malmö, Sweden.

## In the Bookstores



*The Shift – The Future of Work is Already Here*

by Lynda Gratton; HarperCollins Publishers, 2011.

ISBN: 978-0-00-742793-2 (Hardback).  
18.99 GBP. 374 pages.

### Changes and developments in working lives during the next decades

The author of the book *The Shift, The Future of Work is Already Here*, Lynda Gratton, is a professor of management practice at the London Business School. She has been nominated by *The Times* and the *Financial Times* as one of the great business thinkers in the world today. She also takes an active part in a research project aimed at shedding light of the future of work together with 21 global companies and 200 executives. The book takes the reader on a journey to discover how working lives will take form over the next decades. It describes the positive upsides, but also the significant downsides that impact our jobs and careers, and the question is raised of how we will go about crafting our own future working life. The next decades will hold a force that will destroy forever many of the old assumptions of a traditional job and career.

The first part of the book describes five forces that have an impact on the way people's working lives will change and develop over the next decades: technology; globalisation; demography and longevity; society and energy resources. Over the next decades, technology will enable more and more people to work in a joined-up world. Technological advances will lead to mega-companies that span the globe and also millions of smaller groups and partnerships who will create value in emerging 'work ecosystems'. The globalisation opens up an increasing marketplace for cooperation and work. Some people may have the ability to move to creative clusters, but the darker side of change may be the breaking up of families and communities, which may lead to isolation. To reduce energy costs, movement of people and transportation of goods must be significantly reduced.

In the book there are fictitious examples of people living in 2025. There is Jill's storyline – a woman working in the 24/7 joined-up world that never sleeps, leaving limited time to concentrate,

observe, think, and even to play, certainly a fragmented world. Does Jill really have to 'be on' all the time? Then there is Rohan, an Indian brain surgeon. Rohan works from his home office in Mumbai from where he discusses holographic presentations of various brain injuries with a Chinese team. As he speaks, the Hindu language is automatically converted to Cantonese, the spoken language of his Chinese colleagues. For these purposes, he buys access to the Cloud on a day-to-day basis. We also meet Amon, an independent freelancer working from home. The first thing he will be doing is to check with his virtual agent if any new interesting projects are available. What Rohan and Amon share is that neither of them works together with real people during their working day – they do not experience any physical but solely virtual contact with other people throughout their day.

What these people living in 2025 have in common is that they all have a tendency to become isolated. And Jill also has, in addition, the problem of living a fragmented life. What the reader should give a thought is to how these people can learn to make their own choices and, at the same time, avoid succumbing to the pressure of what is expected from them.

In the last part of the book, the reader is given advice on the shifts to think about when aiming at taking the right career path. The first shift is about progressing from being generally skilled to becoming a serial master. Today people have access to the internet and can look up all the general information they want by using Wikipedia® and Google, and thereby they can become a Jack-of-all-trades, which means that they have the opportunity to obtain general skills inside several areas of knowledge. Therefore, if you want to join the talent pool, you have to obtain serial mastery in some specific areas. It is claimed, that it will take you around 10 000 working hours to master a specific discipline. The first shift is also about the ability to change according to the circumstances and to obtain visibility by self-marketing. The second shift refers to individualism and competitiveness versus connectivity with others, collaborations, and networks. You can build up a useful network by connecting with people who can give you new inspiration and ideas, people who are able to support and help you by giving good advice. By building up this

kind of network, you will have the possibility of creating a meaningful working life. The third shift deals with the transformation from being a consumer to becoming an innovative producer.

The book addresses how the future of work is likely to evolve. The ways in which people have been working for the last two decades is slowly disappearing. Having a 9 am to 5 pm working day, knowing colleagues at the office in the company you may have worked for many years and numerous other things will be replaced by new working cultures. This process will happen mainly through the effects of the five forces; the diminishing of carbon-footprints, developments in technology, globalization, demography and longevity, and societal

changes. To keep up with the development, the author poses the question to the reader as whether he or she has taken the necessary shifts towards preparing for the future. One final message in the book is that you 'should go with what you love', which will give you the opportunity to obtain a satisfactory working life. All in all, the book offers a good overview of the working challenges we might all face in future. More about the book, a 'future of work workbook' and interviews with the author can be found at the website: [theshiftbylyndagrattton.com](http://theshiftbylyndagrattton.com).

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"It's the Hendersons. They have a 7:30 dinner date, and want to know if the birth of their son will be any inconvenience."

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## Authorship, ghostwriting, and tips on making scientific writing more enjoyable to read

In this issue five papers are discussed covering the subjects of authorship and authorship criteria, ghostwriting and guest authorship, and adding style to scientific writing.

### *Standards in authorship*

In a short editorial in the BMJ, Baskin and Gross<sup>1</sup>, editors at the journal *Neurology*, returned to the matter of authorship. They discussed a number of issues that have recently come up regarding the authorship criteria of the International Committee of Medical Journal Editors (ICMJE), and whether they are the correct standards with which to measure 'appropriate' authorship. *Neurology* has gone as far as to develop their own authorship policy that departs from the ICMJE criteria and focuses more on a contributorship model; i.e. identifying everyone who contributed to the study, wrote the report, paid for the research, etc. The journal hopes that this will foster greater transparency and disclosure and help avoid honorary and ghost authorship. Briefly, *Neurology's* criteria for authorship are: design or conceptualization of the study, or analysis or interpretation of the data, or drafting or revising the manuscript. In addition, all authors are required to acknowledge all versions; those who do not qualify as authors should be listed as co-investigators or contributors; any paid medical writer who wrote the first draft or responded to the reviewer's comments must be included in the author byline; and finally, all authors must complete and sign authorship forms with roles and contributions, disclosure forms listing all sources of potential bias, and copyright transfer agreements.<sup>2</sup> Baskin and Gross suggest that 'Identification of professional writers as authors is transparent, fair, and anti-discriminatory: credit is given where credit is due.' The authors put forward that scientific research is gradually becoming a more complex and collaborative process, which means increased challenges regarding transparency in authorship and disclosure. They offered that *Neurology's*

policy is a starting point in the effort to improve transparency and suggested that more journals should adopt the contributorship approach in their instructions for authors.

### *Three more articles on ghostwriting*

Rachel Hendrick<sup>3</sup>, in a feature in the BMJ, suggested that ghostwriting in medical publishing on behalf of drug companies has a long history. She gave a few examples, historical (going back to the early twentieth century) and recent, of when large pharmaceutical companies have used professional medical writers to anonymously write articles that portray their product in a favourable light, and then have also paid academics to be named as authors. Hendrick says that this is an issue because of the potential influence on the content and conclusions of the article and leads to problems with data integrity and accountability for the reported research. Hendrick did talk about the possible benefits of using a professional writer; they fill a needs gap, they are able to write well and can increase efficiency. However, she seemed quite dismissive of the value of professional organizations, such as European Medical Writers Association (EMWA), and their codes of practice and qualifications to promote working standards and respect for the profession. There was also the suggestion that even if a writer is acknowledged, this still could be considered ghostwriting, which of course goes against EMWA's current position.

Following on from a 2011 article by Stern and Lemmens<sup>5</sup> (previously mentioned in journal watch<sup>4</sup>) about the possibility of imposing fraud liability for ghostwritten articles, Bosch *et al.*<sup>6</sup> outlined specific models of legal liability that could apply to medical ghostwriting in the USA. Briefly, these areas were: (1) when an injured patient's physician relies on a journal article containing false or manipulated data, the authors could be held legally liable for the injuries; (2) authors of articles used as clinical evidence for indications for off-label uses may be liable as a conspirator under the federal False Claims Act for inducing the US government to reimburse prescriptions under false



pretences; (3) both physicians and sponsor companies may be liable under the federal Anti-Kickback Statute if patients are put at risk by misrepresenting the risk-benefit of a treatment; and (4) although defendants may argue that they have a First Amendment (freedom of speech) right to participate in ghostwriting, the US Supreme Court holds that the First Amendment does not shield fraud. Overall, the authors suggested that the current responses to ghostwriting are unsatisfactory and argue that the only remaining option is the legal system in order to ensure that guest authors take more responsibility for the work they put their names to. How realistic or practical this would be is debatable, especially considering that taking legal action can be both extremely expensive and time consuming.

In a recent commentary, Bosch and Ross<sup>7</sup> debated whether ghostwriting and guest authorship should be seen as research misconduct. They suggested that there are many reasons why academics, sponsors, and medical writers engage in ghostwriting; for example, enhancing professional standing, product promotion, and employment, respectively. They suggested that, at the moment, ghostwriting is perceived as a slight failing or a little bit naughty, rather than as an unethical practice. They went on to say that in this culture, ghostwriting and guest authorship are fool's gold or 'an unspoken permission to fatten curricula with redundant reviews and, predominantly, lower-impact clinical research studies'. Bosch and Ross argued that guest authorship could be seen as a form of plagiarism because using someone's name implies credit for work done by someone else. But the same probably cannot be said for ghostwriting as a ghostwriter 'willingly creates text for attribution to others'. The authors think ghostwriting and guest authorship should be considered acts of research misconduct, as they consider both situations clearly perpetuate a fraud on an unsuspecting public and profession; and feel that professional organizations, such as The Office of Research Integrity, should include ghostwriting and guest authorship in their official definitions of misconduct.

#### *Style and scientific writing*

Advice on how to incorporate style into scientific writing, to make it more enjoyable for the writer

and the reader, was given in an editorial by Franzblau *et al.*<sup>8</sup> The authors said that the communication of study findings is at the core of scientific research; however, medical writing is still often seen as quite dry and formulaic. The authors offered a number of tips on improving the quality and readability of scientific writing. Some of the best ones were: shorter articles are easier to read, most could be considerably shorter without losing the overall message, so authors should edit an article several times to condense the text; try to write in an unambiguous, logical, succinct fashion; use the active voice rather than passive phrases (the grammar tool in word processing programmes can be helpful to highlight passive phrases); reduce repetition by using a thesaurus to provide alternative words; authors should be allowed to use and develop their own personal style of writing; and, there is room for imaginative composition in the introduction, discussion, and conclusion sections of a manuscript, even if the methods have to adhere to strict formats. The take-home message from this article is that the quality of scientific writing needs to improve in order to establish a new, higher standard of literary quality in scientific communication.

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## Open science as a replacement for peer review of scientific articles?

There have been complaints about the peer-review process, but what is the solution? A recent article by Thomas Lin in *The New York Times* (16 January 2012), 'Cracking open the scientific process', discusses 'open science' as a possible solution. Open science means making the results of scientific research freely available and using the power of social networking to replace peer review.

According to the article, some scientists feel that the peer-review system is 'hidebound, expensive, and elitist' and that it should be replaced by open science. These criticisms are probably reasonable. Peer-reviewed journals are expensive to run. However, open science does not completely resolve this problem because professional curation and perseverance of data are time consuming and expensive. The 'hidebound' and 'elitist' criticisms are a bit vague and are not really addressed in the article. Probably they mean that there can be a political side to getting published – who the authors are and their institutions they are affiliated with can affect the ability to be published, when it is the quality of the science alone that should really be the deciding factor. The criticism is also probably made because reviews are sometimes insufficient so that bad science gets published, whereas good, innovative science is sometimes blocked because it contradicts existing dogma. Although improvements are being made, publishing research results *should* be better, faster, and cheaper and should take better advantage of electronic media.

As examples of open science, the article mentions online-only journals like *Nature Communications* ([www.nature.com/ncomms/](http://www.nature.com/ncomms/)), and the PLoS journals ([www.plos.org/](http://www.plos.org/)). These journals simply do not charge for access, although they charge the authors for submitting an article. These are faster to print, and open access is a great way to catalyse the sharing of scientific information, but these journals do not eliminate peer review and therefore do not truly constitute open science.

The article also mentions ResearchGate ([www.researchgate.net/](http://www.researchgate.net/)), an interactive website, where scientists can pose and answer questions from other scientists. This website is great for sharing ideas, but it is not currently a site for publishing the results of research or for peer review of those results. Moreover, sharing of ideas is not the same as a true in-depth critique of study results. On the other hand, using the Internet for post-publication review of research is a great idea.

Unfortunately, the *New York Times* article does not explain or provide examples of how open science could replace professional peer review, nor does it address whether eliminating peer review is a good idea. Even with many people critiquing an article through a social networking site, whether it is possible to attain the same depth of review as using two or three dedicated peer reviewers is not yet clear. Also, experience with Wikipedia<sup>®</sup> shows that using social networking in place of true peer review carries certain risks for abuse and misinformation.<sup>1-3</sup> So it is not yet clear, at least from the *New York Times* article, how or why open science would be better than professional peer review.

For the moment, peer review is the only system for the in-depth evaluation of research and the conclusions made from it. Open science seems to be a great way to improve information sharing and access to published research, but whether it is a good replacement for peer review remains to be seen. Changes are coming, but what they will look like is not yet obvious.

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## Cause: Its effect on biomedical research

Jonah Lehrer contends that we jump to conclusions about causation too quickly and explains his

reasoning in his article 'Trials and errors: Why science is failing us'.<sup>1</sup>

He challenges the assumption that ever deeper research of a system to discover subtle correlations

will reveal how the entire system works. The article is certainly a thought-provoking read for anyone interested in biomedical research, especially against the background given by Lehrer that R&D costs of discovering a new drug are about 100 times higher (adjusted for inflation) than in the 1950s and development takes three times as long. Even more disheartening is that 'According to one internal estimate, approximately 85 percent of new prescription drugs approved by European regulators provide little or no benefit'.

Lehrer illustrates that causes are inferences rather than facts by referring to experiments conducted in the 1940s by the Belgian psychologist Albert Michotte which showed how humans observe a series of events and form conclusions that one thing causes another. For example, if one rolling ball touches another and the other ball moves, the first ball is assumed to have caused the second one to move. People thus translate perceptions into causal beliefs.

In scientific research, statistical correlation has been developed to show associations between measurements and the assumed cause. But Lehrer points out that reliance on correlations has entered an age of diminishing returns. The easy causes have been found and scientists are forced to search for the tiniest of associations but too often rely on simple correlations and fail to make the effort to search for secondary and tertiary interactions in these systems. Lehrer gives a number of examples of this failure starting with Pfizer's withdrawal of the drug troceta-pib after it had entered phase III clinical trials. The withdrawal was announced 2 days after the company's CEO had stated that this new cholesterol-lowering drug would be 'one of the most important compounds of our generation'. Instead of preventing heart disease it was found to lead to a 60% increase in mortality. Lehrer concludes that because the individual steps of the cholesterol pathway were well understood false assumptions were made about how the pathway functions as a whole.

Another example he gives is back pain from which 80% of us will suffer at some point in our life. Doctors used to tell their patients to take time off and rest in bed. Ninety per cent of patients with lower back pain recovered within 6 weeks. However, magnetic resonance imaging was introduced in the 1970s and showed a strong correlation between back pain

and seriously degenerated spinal discs. Doctors changed tack to prescriptions of epidurals and surgical removal of the damaged tissues. Subsequent research found disc abnormalities were just as likely to be correlated with no pain and a recent study found that a small subset of non-spinal factors such as smoking and depression were more closely associated with serious back pain. Another illustration he gives is biomarkers where a study has now found that 83% of supposed correlations become weaker with further studies.

The readers' comments on the article variously accuse Lehrer of being provocative, anti-science, and praise him for being brave. He is charged with promoting holistic medicine, the prospect of which seems to be like a red rag to a bull for many medical practitioners, and then defended against having done so. A few comments from readers are worth quoting:

The nature of publishing has also changed such that scientists are encouraged to publish piecemeal rather than wait for Ultimate Certainty before submitting a study for publication. On the plus side this keeps a good flow of information rolling, but on the minus side it means the likelihood of being inaccurate, or downright wrong, proportionally increases.

If anything your examples only reinforce the point that sufficiently powered, double-blind studies are the only check we have against our frequently incorrect assumptions and intuitions about causality.

The pharmaceutical industry is looking for answers, but is starting from the wrong place. Without understanding the mind's effect on the body we'll never come up with consistently effective therapies.

Science is, in fact, not failing us at all; rigorous experimental design (e.g. Phase III clinical trials) are defeating the poor initial research.

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## The higher the income the lower the morals

Medical writers are it is to be hoped concerned about ethics. For this reason, an article published in PNAS earlier this year should be of some interest to us. The article reports five studies undertaken in naturalistic and experimental settings with social class as the major variable. The studies found that upper-class people are more unethical than lower-class people.

The investigators concluded that abundant resources and elevated rank give upper-class people the freedom and independence from others which causes them to prioritize self-interest over the welfare of others. Furthermore, rich people

perceive greed as positive and beneficial, which the authors contend flows from economics education with its focus on maximizing self-interest. These upper-class attitudes result in a higher tendency to unethical behaviour among the rich than among the poor. The relative independence from others and increased privacy in their professions result in fewer constraints and less perceived risk associated with committing unethical acts, added to which such people have a feeling of entitlement.

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## Recommendations for improving the reporting of industry-sponsored studies

A commentary recently published in the *Mayo Clinic Proceedings*<sup>1</sup> by The Medical Publishing Insights and Practices (MPIP) will be of interest to medical writers working with publications in the pharmaceutical industry. It makes the following 10 recommendations for closing the credibility gap in reporting industry-sponsored clinical research:

1. Ensure clinical studies and publications address clinically important questions.
2. Make public all results, including negative or unfavourable ones, in a timely manner, while avoiding redundancy.
3. Improve understanding and disclosure of authors' potential conflicts of interest.
4. Educate authors on how to develop quality manuscripts and meet journal expectations.

5. Improve disclosure of authorship contributions and writing assistance and continue education on best publication.
6. Practices to end ghostwriting and guest authorship.
7. Report adverse event data more transparently and in a more clinically meaningful manner.
8. Provide access to more complete protocol information.
9. Transparently report statistical methods used in the analysis.
10. Ensure authors can access complete study data, know how to do so, and can attest to this.
11. Support the sharing of prior reviews from other journals.

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## We like your article, but there's one small thing you could do for us ... The problem of coercive self-citation

Have you heard of editors trying to get authors to cite more articles published in their journals? US researcher Eric Fong had not, until it happened to him.

Teaming up with fellow academic Allen Wilhite, he decided to investigate the scale of the problem, which the two of them refer to as 'coercive self-citation' and define as a request to add unspecified citations from the editor's journal. Their findings were published in the February issue of *Science*.<sup>1</sup>

Wilhite and Fong invited over 50,000 academics in business, economics, sociology, and psychology to participate in a survey<sup>2</sup> to find out how many had heard of this practice and how many had themselves been affected by it.

Of the 6672 people who responded, some 40% were aware of coercive self-citation and 20% had personally encountered it.<sup>1</sup> Further analysis showed that junior researchers were more likely than senior ones to give in to an editor's demands, and that journals with commercial publishers were more likely to coerce than those published by academic societies.

Contributing to a follow-up piece on the *Nature* website,<sup>3</sup> publishing consultant Phil Davis highlights possible sources of bias in the study – e.g. responders potentially being more likely than non-responders to be aware of coercion by journal editors – but ultimately accepts that the problem exists.

The editors of the two journals that were most commonly named by responders as engaging in coercive self-citation unsurprisingly deny involvement in this kind of activity.<sup>3</sup>

Citations are the basis for journal impact factors. Referencing a couple of articles published in *Journal of X Y* to keep the demanding editor happy may seem trivial to the author who does it, but impact factors are a big deal. Academic careers depend on them.

Earlier studies have highlighted serious impact factor abuses. In one notable incident, a journal managed to increase its impact factor by 18 ranks by publishing a single article that cited a jaw-dropping 303 of the journal's previous papers.<sup>4</sup>

In an earlier case,<sup>5</sup> authors who submitted a manuscript to the journal *Leukemia* received a letter containing the following request: 'We have noticed that you cite *Leukemia* [once in 42 references]. Consequently, we kindly ask you to add references of articles published in *Leukemia* to your present article'.

It is by no means the only such example.<sup>6</sup>

Marie McVeigh, director of Thomas Reuters' Journal Citation Reports, feels that the figures reported by Wilhite and Fong are higher than she would have expected based on her own data. Nonetheless, Thomas Reuters has taken steps to address the problem. It now publishes impact factors with *and* without self-citations and temporarily delists journals that have used self-citation to boost their impact factors.<sup>7</sup>

But is this enough? Should self-citations be removed from impact factors altogether? While Wilhite certainly advocates this change, he does acknowledge the need for studies of other disciplines (including biological sciences). And he is yet to secure McVeigh's support.

For the record, I can honestly say that I have never been put under pressure to cite *TWS* articles when writing for this journal!

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# The Webscout

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## Issues in paediatrics

Infants, children, and adolescents have special needs regarding their health and care. They are not 'little adults'. The spectrum of illnesses differs from that known in adults. Just think of teething problems like chicken pox, measles, or scarlet fever. Sure, these infections can also trouble adults, but usually have a peak in childhood. Some very rare illnesses only occur in children or start in early infancy. This especially applies to genetic diseases, so have you ever heard of Gaucher disease or Legg-Calve-Perthes disease? ADHD, the attention deficit hyperactivity disorder, is diagnosed with increasing frequency, which is heavily discussed and questioned. Other illnesses are rather unknown in children like osteoporosis, dementia, or heart attack. Further diseases that once presented in adults only are now on the rise in children and adolescents. Our Western life style boosts obesity and hence type 2 diabetes and arthrosis, for example, are now already affecting the young generations.

Apart from the need for special medications for children's diseases, children need adaption of dosing and suitable application forms. Up to now, most medications have not been licensed for use in children. This is why the Paediatric Investigational Plan emerged. It should help to provide safe drugs with safe dosing for children. Currently, however, paediatricians are often confronted with off-label use of drugs. Doctors feel unsecure and medication errors are frequent and suitable application forms are often missing.

Apart from all these issues, the most unsettling thing we are confronted with in paediatrics is chronic and severe illnesses leading to death at a young age. Palliative and psychological end-of-life care has to be tailored to the little patients and the way they see the world.

The following links give you a first impression of the complexity of health care in children and adolescents:  
[http://rarediseases.about.com/od/rarediseasesadu/Pediatric\\_Diseases.htm](http://rarediseases.about.com/od/rarediseasesadu/Pediatric_Diseases.htm)

This webpage gives some explanation on quite a few rare diseases you might have never heard about.

The contents are designed for non-professionals, yet I think, this is a good point to start from in order to broaden your knowledge of rare diseases.

[http://pediatrics.about.com/od/diseasesandconditions/Common\\_Pediatric\\_Diseases\\_and\\_Conditions.htm](http://pediatrics.about.com/od/diseasesandconditions/Common_Pediatric_Diseases_and_Conditions.htm)

This is the pendant to the webpage described above, covering common diseases. The term 'common' is interpreted in a broad way, so you will find illnesses described which you probably would not have expected to be common. It is not only about measles and chicken pox. You will also find information on, for example, childhood cancer or autoimmune diseases.

<http://www.pediatriceducation.org/casesbydisease/>

Here you can find case reports of children of different ages. For some of the cases you will find information on possible differential diagnosis depending on age. The case reports are easy to read and short enough just to have a quick run through it. And they illustrate how complex diagnosing diseases in children really is.

<http://www.help4adhd.org/en/about/myths>

A great controversy exists about ADHD, the attention deficit hyperactivity disorder. A matter of debate is whether ADHD is over-diagnosed and children over-medicated. However, ADHD can be a serious neurological illness enormously affecting the daily life of a family. Read about the myths and misunderstandings around ADHD on this page. Further contents on this website are worth reading as well. By the way, ADHD not only affects children but also presents in adults.

<http://www.editorsweb.org/children/how-drugs-work-in-children.htm>

This is a short summary of the specialities of drug use in children with respect to kinetics, toxicity, and application. As said before, pharmacokinetics in children are very different from those in adults and depend on age. It is crucial to know about this when prescribing off-label for use in children.

<http://www.pediatricsdigest.mobi/content/113/2/381.full.pdf+html>

In end-of-life care in children and adolescents you have to consider certain aspects that usually do not play a role in adult palliative care. From the moral point of view, it seems clear that patient preferences regarding treatment or especially end of treatment should be taken seriously. But legally, the patients lack the authority to decide upon this. Apart from these legal aspects, communication plays a very important role. Medical information needs to be

communicated in a way a child or adolescent can understand and cope with from a psychological point of view. This heavily depends on age and the developmental stage. The linked article gives you a summary of issues in palliative care in young patients.

If you have any further questions or you have any other comments or suggestions, please email me at: [karin.eichele@novartis.com](mailto:karin.eichele@novartis.com).

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# Manuscript Writing

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## Guidelines for manuscript writing: Here to help

Although sometimes maligned, guidelines make manuscript writing easier and increase the chances of getting published. A good set of guidelines can be used as a checklist (many even include checklists) to help organize, write, format and submit a manuscript.

Manuscript writing guidelines are sets of instructions put together by journal editors and other experts to help ensure that all manuscripts attain a uniform level of quality and ethics. Guidelines can also answer questions, help avoid pitfalls, and ensure that the manuscript is in agreement with standard medical writing practice. In this way, guidelines can reduce the chance that your manuscript is rejected and they help save time. Following guidelines can also improve the chances that the results are included in systematic reviews and meta-analyses.

Although guidelines are important, they are not laws. They often have to be adapted to the specific needs of the manuscript. In some cases, guidelines will insist on something that you consider irrelevant. Regardless, they can be of great help in reducing the number of problems and amount of time spent in completing a manuscript.

Following is a list of the key guidelines used for manuscript writing. The different guidelines and their contents are also summarized in Table 1.

## General guidelines for manuscripts

### *Instructions for authors*

The instructions for authors might seem like an obvious guideline to follow, but surprisingly, many submitted manuscripts do not fully comply with them. This is a potential reason for rejection – or at least a source of irritation for editors and reviewers. Although a checklist is not normally part of the instructions for authors, it's a good idea to print them out and use them as a quality control checklist before you submit your manuscript.

### *ICMJE Uniform Requirements for Manuscripts*

The International Committee of Medical Journal Editors (ICMJE; <http://www.icmje.org>) publishes the Uniform Requirements for Manuscripts.<sup>1</sup> These

are some of the most useful general guidelines for preparing a manuscript for submission to a journal, and all manuscript writers should be aware of their content. The uniform requirements include specific instructions on:

- What should be included on the title page and in the abstract, introduction, methods, results, and discussion.
- How to cite references, prepare illustrations, and use abbreviations.
- Ethical reporting of research, including authorship, the role of contributors, disclosure of conflicts of interest, privacy and confidentiality, and protection of human subjects and animals in research.

### *EASE Guidelines for Authors and Translators of Scientific Articles to be Published in English*

The Guidelines for Authors and Translators of Scientific Articles to be Published in English,<sup>2</sup> published by the European Association of Science Editors (EASE; <http://www.ease.org.uk/>), are intended to help non-native English manuscript writers, although they could really be used by any manuscript writer. These guidelines explain:

- How to write completely, concisely, and clearly in English?
- What should and should not be in each section of a manuscript?

The guidelines also include detailed appendices covering the key elements of abstracts; how to avoid ambiguity and build cohesion in English writing; ethics; the use of plurals; how to simplify English text; and differences between spelling in American and British English.

To help non-native English writers, the guidelines are available in 16 languages in addition to English.

## Reporting guidelines

### *Reporting of randomized clinical trials: the CONSORT statement*

The CONSORT statement<sup>3</sup> is probably the most important set of guidelines for most manuscript



Table 1: Guidelines for manuscript writing

	General guidelines			Reporting guidelines					Ethics guidelines			
	EQUATOR Network	Instructions for authors	ICMJE Uniform Requirements	EASE Guidelines	CONSORT Statement	PRISMA Statement	MOOSE Statement	STROBE Statement	TREND Statement	GPP and GPP2	EMWA Guidelines	CSE White Papers
Manuscript organization	•	•	•									
Tips on writing manuscripts	•			•								
Content of each manuscript section	•			•								
All articles	•	•	•									
Randomized clinical trials	•			•								
Systematic reviews and meta-analysis	•				•							
Observational studies	•							•				
Non-randomized studies	•								•			
Text format: font, spacing, length, etc.		•										
Instructions for making figures and tables		•										
Authorship and acknowledgments	•		•							•	•	•
Conflicts of interest	•									•	•	•
Use of medical writers and ghost writing	•									•	•	•

writers. The objective of the CONSORT statement is to enable ‘readers to understand a trial’s design, conduct, analysis and interpretation, and to assess the validity of its results’. In other words, the goal is to ensure complete transparency from the authors.

The most useful part of the CONSORT statement is the CONSORT checklist, which is a detailed list of exactly what should be in each section of a manuscript reporting a randomized clinical trial. This is especially important for the complete and accurate reporting of the methods and results.

The CONSORT statement also details how to describe the flow of patients through the clinical trial. In particular, they recommend using a patient flow diagram and they provide an example. This flow diagram is often referred to as a ‘CONSORT diagram’.

In some cases, it will not be relevant or possible to fulfill all of the items for all studies, so adapt the guidelines as needed. Furthermore, although the CONSORT statement is intended for reporting randomized clinical trials, it can be adapted to other study designs.

*Other key reporting guidelines*

Several guidelines have been published for reporting studies with a non-randomized design. Some of the most important guidelines include the following:

- *STROBE Statement*.<sup>4</sup> These are guidelines for reporting observational studies. They include a checklist for what should be included in each section of the manuscript.
- *TREND Statement*.<sup>5</sup> These are guidelines for reporting studies with non-randomized designs. They include a checklist for what should be included in each section of the manuscript.
- *PRISMA Statement*.<sup>6</sup> These are guidelines for reporting systematic reviews and meta-analyses. They are mainly intended for systematic reviews and meta-analyses of randomized clinical studies but can be adapted to other types of studies.
- *MOOSE Statement*.<sup>7</sup> These are guidelines for reporting systematic reviews and meta-analyses of observational studies. Note that the MOOSE statement has not been updated since its original publication in 2000, so to ensure completeness, you might also consider referring to the PRISMA statement if writing a systematic review or meta-analysis of observational studies.

*EQUATOR network*

The EQUATOR network (<http://www.equator-network.org>) deserves special mention because it

contains a wide variety of resources for the reporting of medical research and is especially helpful to manuscript writers. No matter what kind of article you are writing, you should be able to find a link to a relevant guideline in the EQUATOR resource center (<http://www.equator-network.org/resource-centre/library-of-health-research-reporting/>). The use and aims of the EQUATOR network was previously discussed in detail in a 2009 article in *The Write Stuff* by Catherine Mary.<sup>8</sup>

## Ethics guidelines for manuscript writers

### *EMWA Guidelines on the Role of Medical Writers in Developing Peer-Reviewed Publications*

In 2005, EMWA published ethical guidelines for medical writers who prepare manuscripts on behalf of named authors.<sup>9</sup> In part, these guidelines were intended to help address the problem of 'ghost authorship'. The guidelines also cover the nature of the relationship between the medical writer and the study sponsor and authors; whether medical writers should list authors and, if not, how they should be acknowledged; the writers' professional and ethical responsibilities; and access of medical writers to study data.

### *GPP and GPP2*

Good Publication Practice (GPP),<sup>10</sup> published in 2003, was developed by the Council of Science Editors 'to ensure that clinical trials sponsored by pharmaceutical companies are published in a responsible and ethical manner'. In particular, they provide guidelines to help avoid publication bias and to clarify the relationship between pharmaceutical companies and academic investigators. In particular, GPP gives guidance on publication standards, disclosure of potential conflicts of interest, what constitutes unacceptable prior or concurrent publication, identification of clinical trials, authorship, and the proper role of professional medical writers. GPP2 was a 2009 update of GPP<sup>11</sup> and is a refinement of the positions stated in GPP. A detailed discussion and critique of GPP2 was published in 2009 by Nancy Milligan and Adam Jacobs in *The Write Stuff*.<sup>12</sup>

### *Council of Science Editors white papers*

The Council of Science Editors (<http://www.councilscienceeditors.org>) has published a series of documents covering their editorial policies. These include guidelines on author and sponsor responsibilities, who should be an author, who should

receive an acknowledgment, and disclosure of potential conflicts of interest.<sup>13</sup>

## Summary

Guidelines are to help you write a complete and accurate manuscript and therefore to increase the chance that your manuscript is accepted and read. All manuscript writers should be aware of and use them in the preparation of manuscripts. They are not laws, but they are excellent sources of guidance and instruction.

## Acknowledgments

I would like to thank Elise Langdon-Neuner for background information that helped form the basis of this article.

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## A comprehensive plagiarism and ethical writing guide

Recently when working with a junior writer on an article, I noticed that they had copied and pasted several chunks of text that were not their own. Although there are apparently cultural differences in how plagiarism is viewed, plagiarism is not acceptable for manuscripts; it is considered unethical and a definite reason to have your manuscript rejected.

To help students and new writers understand plagiarism and other ethical issues around scientific writing, Dr Miguel Roig of the Office of Research Integrity at St John's University wrote 'Avoiding plagiarism, self-plagiarism, and other questionable writing practices: A guide to ethical writing'. This

is an excellent and comprehensive document and can be accessed for free on-line at <http://facpub.stjohns.edu/~roigm/plagiarism/>.

This detailed guide covers not only plagiarism but also 'other crimes of writing', including ethically questionable citation (referencing) practices (especially careless referencing), ethically questionable writing practices (e.g. selective reporting of results), and authorship and conflicts of interest. The guide also includes 15 pages of exercises to help teach the issues discussed in the first 49 pages. Although the printed version is a long read, it is an excellent reference and teaching resource – and fortunately – the on-line version includes a home page with hot links to each of the specific topics.

## Publishing in a digital world: Strategies to maximise visibility and citations

The world of academic publishing has changed enormously over the past two decades. As a student in the mid-1990s, I have fond memories of library study sessions surrounded by shelves bowing with the weight of knowledge. A less positive recollection is trying to flatten the thick, bound journals under the photocopier lid. Nowadays students and researchers rarely visit the library, instead accessing research articles almost exclusively online.

The shift from print-driven to online journals requires minor, yet important changes in writing style to raise the visibility of an article and therefore maximize the likelihood it will be downloaded and cited.

After 40 years as a print-driven journal, *Politics & Policy* (Wiley-Blackwell) entered 2012 as an online only, subscribed-access publication. In an excellent article,<sup>1</sup> the editor summarizes the benefits of

online distribution and then details five strategies to enhance an article's profile in the online environment.

Most importantly, you want people to find your article, so choose a search engine-friendly title. Bear in mind that it is a machine that conducts the preliminary sort and humans the second, so save clever puns for subheadings. The best are narrative titles that capture the essence of the article and include keywords.<sup>2</sup> Perhaps surprisingly, articles with longer titles tend to be cited more than those with shorter ones.<sup>3</sup> Take time to settle on a title and trial its impact by running searches in various engines; be prepared to refine it.

To tempt further reading and download, invest time in writing structured abstracts.<sup>4</sup> Repeating keywords and phrases that were used in the title will boost search engine rankings. Excellent examples of effective and less effective abstracts are provided by Wiley-Blackwell Author Services.<sup>5</sup>

Structure the main body of the text using subheadings to enable straightforward navigation

using 'jump to' access and ensure that your article is fully connected to the literature in which it is embedded. Writing an engaging, comprehensive literature review can increase the chances of citation. Cite a range of articles, books, and online data sources; the numbers of pages to which articles are connected also feature in the result-ranking algorithms of search engines. To enable reference-linking, provide all the webpages of the articles cited and, where relevant, the dates accessed.

Bring your research to life by using media and links creatively. Gone are the days when a coloured graph was sufficient to impress; now it's videos, podcasts, sound files, and animations. For further ideas, check out 'The Periodic Table of Visualisation Methods'.<sup>6</sup> Novel and exciting ways of representing data will lead both to increased citation and encourage download by those seeking tools for teaching. Resources and editing software are freely available.<sup>7</sup>

Lastly, raise the profile of your research by disseminating your published article as widely as possible. The more connections to your article, the higher it will rank in search engine results. Do not be modest: send your article to colleagues and broadcast your research to the world using the plethora of modern communication and educational tools, including Twitter, Moodle, and Wikipedia, to name just a few. Many excellent resources exist to help launch one's online presence.<sup>8,9</sup>

A new world of journal publishing is rapidly unfolding. While some of the suggested adaptations may seem daunting, perhaps particularly the adoption of social media, taking a step back to consider and modify one's approach to publishing online will undoubtedly reap rewards.

Reviewing this article has certainly given me food for thought. I am particularly excited by the opportunity to use different media, but what will I do with my empty shelves?

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## Retractions and misconduct: *science* presents the lessons it has learnt

The Committee of Publication Ethics (COPE) held its annual European seminar in London on 16 March 2012. The important topic, 'Correcting the literature', aligns with COPE's retraction guidelines for editors.<sup>1</sup>

A highlight of the seminar was the presentation given by Andrew Sugden, Deputy Editor of *Science*. He started by defining the good, the bad and the

ugly authors in the context of retractions: good authors initiate the process, usually by writing to the editor with a request for retraction because they have discovered an error. Bad authors are those who when a retraction is appropriate refuse to sign the retraction and the ugly refuse to retract despite their institution's findings of misconduct. In *Science* the good outweigh the rest. From the reaction of medical journal editors in the audience this might not be the case for their journals.

The past 10 years have seen a jump of more than 15-fold in the number of published papers retracted from scientific journals. Sugden had traced the first retraction published in *Science* back to 1963. In the 1990s the journal retracted eight papers. Between 2000 and 2010 there were 50 retractions including the infamous eight papers authored by the physicist Jan Hendrik Schön and the two by the stem cell researcher Woo Suk Hwang. About a third of *Science's* retractions have been for misconduct, the rest for seemingly honest error. The mean time from initiation of investigations to retraction in *Science* is 2.8 years (maximum 8 years). An expression of concern, of which *Science* has published eight, indicates an investigation has been initiated or the journal has worries. The journal might be alerted to a problem by an anonymous whistle blower, the corresponding author (self), co-authors, an identified or unidentified correspondent, and an author's institution or a reviewer.

Investigations have to be handled sensitively bearing in mind language barriers, the involvement of multiple institutions/countries and the human element of co-authors. Attempted suicide and hospitalizations may have been provoked by such investigations. Sugden also warned of the danger that intense media scrutiny can lead to a journal acting too fast.

The wording of retractions is important. They should be informative stating why the retraction is being made rather than a bland statement that the data are no longer reliable as in the following example given by Sugden 'I have decided to retract the paper "Virus specific splicing inhibitor in extracts from cells infected with HIV-1" - by D. Gutman and myself published on 16 September 1988 issue of *Science* (volume 241, p. 1492). The data in that paper should no longer be considered reliable. Carlos J. Goldenberg'.

A retraction might be of a part or of the entire paper. Partial retractions are very rare, and often relate to interpretation. In a recent case a paper was partially retraction because samples were contaminated. *Science* published an expression of concern in July 2010 relating to the paper in which the researchers claimed to have found an infectious retrovirus, XMRV, in the blood of patients with chronic fatigue syndrome (CFS). Three laboratories had contributed to the study. However, as stated in the expression of concern, at least 10 other laboratories were unable to detect the virus.


In September the authors published a partial retraction of a figure and supplemental figure and table, all of which presented data from contaminated samples. Subsequently the journal lost

confidence in the paper altogether and most authors agreed to a full retraction but consensus on the wording of the retraction could not be reached between the editor and all the authors. As a result the editor himself took the rare step in December 2011 of retracting the article stating that multiple laboratories, including those of the original authors, had failed to detect the virus in CFS patient. Furthermore there was evidence of poor quality control of the experiments.<sup>3</sup> A complicating element in this case was pressure against retraction from patient's groups which had hailed the paper as allaying skepticism about the existence of the disease.

*Science* retracted two papers in 2006 published by a group at Seoul National University led by Woo Suk Hwang.<sup>4</sup> In the papers the researchers claimed that they had created stem-cell lines from cloned human embryos. This caused a sensation because it raised the prospect of using stem cells genetically matched to patients to cure debilitating disorders such as Alzheimer's or Parkinson's. Investigation of the papers was prompted by anonymous information received by the journal casting suspicion on images presented in one of the papers. Hwang eventually admitted that the data had been falsified; the cells were not cloned but were from in vitro fertilization embryos.

*Science*, Sugden said, had been shaken by the Hwang case. The journal commissioned an investigation as a result of which the editors were satisfied that the peer review had been thorough. The report produced, *Science's* response and an editorial are available on the science website.<sup>5</sup> As a result of the report *Science* put the following safeguard procedures in place:

1. All authors are notified by the journal when a manuscript with their name on it is submitted. About once every two weeks authors say they did not know about the submission and when this happens the manuscript is rejected until the authors sort out the problem.
2. Authors are required to complete a detailed form giving their level of participation and a conflict of interest form must be completed by all authors, not just the corresponding author.
3. The senior author from each group is required to have examined the raw data their group has produced.
4. The journal seeks to minimizing restrictions on data access by requiring that all authors agree to the data being available for inspection. The general information for authors includes a



## To retract or not to retract?

	Correction	Expression of Concern	Retraction	No action / Self-correcting scientific process	Letter or Technical Comment exchange
Results unrepeatable	x	x	x	x	x
Data not available	x	x	x		
Fabrication/ plagiarism		x -> -> ->	X		
Interpretation/ conclusions questioned			x	x	x
(lack of) citation	(x)			x	

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statement that is far more reaching than anything that can be found in medical journal author guidelines: ‘All data necessary to understand, assess and extend the conclusion of the manuscript must be available to any reader of Science’.<sup>6</sup> Of special note is the word ‘extend’ in this statement.

- The journal checks all figures at revision for inappropriate adjustments.

Had these precautions helped? Sugden’s comment was that no great difference can be seen between the retraction rate before and after the Hwang case.

Papers attract more scrutiny from the journal if they are multidisciplinary or a number of different laboratories and/or countries are involved. These are fertile factors for insufficient consultation, which can result even in honest error. Other aspects that might give rise to suspicion are where the results are too good to be believed or if the journal requests additional experiments/data which are produced extraordinarily quickly.

Recent years have seen an increasing trend for more supplemental material published with articles.

This broadens the scope for suspect material and raises the question of whether this data gets the scrutiny it needs. *Science* tries to ensure the data are always essential to the integrity and quality of the paper, while one journal has even decided not to accept supplemental anymore.

The slide below, kindly provided by Andrew Sugden from his presentation and reproduced with his permission, summarizes the action that he and his colleagues take when irregularities or errors in published papers come to light.

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## Retraction Watch

Although it is possible to search MEDLINE and the Web of Science for retractions there is no single database of scientific article retractions. The best way to keep abreast of retractions is to visit or sign up to receive alerts from the Retraction Watch blog (<http://retractionwatch.wordpress.com/>). The blog was set up in August 2010 by two American medical reporters Adam Marcus and Ivan Oransky. The blog is reader-friendly and provides regular information about retractions and the fate of authors whose articles are retracted.

In future CrossMark (see below) should also make it easier to identify articles that have been retracted.

## CrossMark: Communicating article metadata to readers

Is a new initiative from CrossRef to communicate information about an article to readers. It will be particularly useful for communicating corrections and retractions. Although a retraction or correction will be noted on PubMed and the publisher's websites up until now the first articles brought up by a Google search might not indicate such post-publication changes. The pilot can be viewed on <http://crossmarksupport.labs.crossref.org>.

Any document that has a DOI (often assigned on acceptance of a manuscript) including online early articles, pdfs, HTMLs, and abstracts can have a CrossMark. When the viewer clicks on the CrossMark logo a box pops up giving the status of the article with, for example the publisher, publication date, and DOI. By clicking on another tab a record is displayed giving metadata, for example if it has been peer reviewed, its publication history and copyright holder, funding disclosures. The status will also indicate updates, for example a correction to the paper.

## Open peer review

Throughout 2012 Elsevier will be piloting a project with their Agriculture and Forest Meteorology

articles. Peer reviewers' comments will be published with articles on their SciVerse ScienceDirect portal. Reviewers will be informed before their comments are published and given the option of having their name included with the comment. It is hoped that this step will attract better reviewers (only good quality reviews will be published) and improve the value of the articles. If successful the intention is to extend the project to other journals in their portfolio in due course.<sup>1</sup>

Evidence that open review improves the quality of reviewers' comments comes from a study conducted at the John Hopkins Bloomberg School of Public health by Jeffrey T. Leek and co-workers.<sup>2</sup> They used an online game to compare open and closed peer review and found that when the reviewers' anonymity was removed from the review process reviewers spent more time reviewing, their reviews were more accurate and they formed significantly more cooperative interactions with authors, all of which could lead to a decrease in the risk of errors in reviewing.

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## Citing tweets

If you have not needed to know by now you probably will do sooner than you had thought. The answer to the question 'How do I cite a tweet?' is given on the Modern Language Association website ([http://www.mla.org/style/handbook\\_faq/cite\\_a\\_tweet](http://www.mla.org/style/handbook_faq/cite_a_tweet)). It recommends that the tweeter's

real name is given followed by the user name in parenthesis, but without parenthesis if the real name is not used on Twitter. The full text of the tweet should be given within inverted commas followed by the date and time of the tweet as read on the Twitter received. The example give on the site is:

Athar, Solhaib (ReallyVirtual). 'Helicopter hovering above Abbottabad at 1AM (is rare event)'. 1 May 2011, 3:58. Tweet.

The following suggestions are made for the manner in which the tweet can be quoted in the body of the text:

Solhaib Athar noted that the presence of a helicopter at that hour was 'a rare event'.

or

The presence of a helicopter at that hour was 'a rare event' (Athar).

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## The Global Alliance of Publication Professionals

I am very proud to be able to tell EMWA members that I have recently become involved in a new initiative, the Global Alliance of Publication Professionals (GAPP). GAPP, which consists of myself, Karen Woolley, Cindy Hamilton, Art Gertel, and Gene Snyder, has been set up as a "rapid response force" to deal with stories about medical writers on blogs and in traditional media.

You will doubtless be aware that many negative articles are written about medical writers, particularly in the context of their role in publications in peer-reviewed journals, and often fail to make the crucial distinction between ghostwriters and professional medical writers. GAPP exists to respond to such articles, to educate those who misunderstand what medical writers do, and to be a resource for journalists who need an authoritative source within the medical writing community.

Why do we need GAPP when we already have splendid organisations like EMWA? Organisations like EMWA, AMWA, and ISMPP can and do respond to articles in the press, but they tend to be slow as they usually like to have any statements bearing the organisation's name to be approved by committees. There is therefore a risk that the news

cycle has moved on by the time the response has been approved. Individuals like me also respond to stories, and can do so rapidly, but a response from an individual doesn't have quite the same authority as one from an organisation. GAPP is designed to give the best of both worlds.

GAPP was launched officially at the beginning of February, and has already been active in responding to stories. You can read a couple of our early contributions at <http://bit.ly/f7dCnA> and <http://bit.ly/ybAoqq>.

You can read more about GAPP at <http://gappteam.org/> and you can follow us on Twitter at @GAPPTeam. You can also join our LinkedIn group by following the link from our website.

If you spot any stories in the media that you think merit a GAPP response, then please let us know, either on Twitter or by emailing us at [contact@gappteam.org](mailto:contact@gappteam.org).

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## The Physicians Payment Sunshine Act – casting a shadow over clinical research?

In October 2010, the American congress passed the Physicians Payment Sunshine Act, which will force drug and medical device manufacturers to disclose their payments to healthcare professionals (HCPs). Starting this year, drug makers are required to track all payments to HCPs and from September 2013 onwards, details of these payments will be made freely available on the Internet for all and sundry to analyse. In other countries too, for example the UK with the new Association of the British Pharmaceutical Industry (ABPI) code of practice update, drug companies will be forced into disclosure, though the requirements are usually somewhat less stringent. In response, pharmaceutical companies have been scrambling to become compliant. This is no mean feat, given the complexity and extent of the relationship between drug companies and HCPs. In particular, large drug companies operate in many different countries with many different business cultures and attitudes, and under many different legislative frameworks.

Ostensibly, the main target of these changes is the marketing end of the pharmaceutical business. Although the free gifts handed out to physicians by drug reps are already more tightly regulated, drug companies still spend large sums of money, for example, on key note speakers at satellite symposia in medical congresses (thereby obtaining an indirect form of endorsement) and other forms of promotional activity. The argument goes that these large budgets are ultimately passed on to the consumer in the form of higher drug prices. Aggressive marketing could also persuade doctors to prescribe expensive new proprietary medicines when a cheap generic alternative would be perfectly acceptable. The greater transparency and awareness of how much money is actually spent by the drug companies will, according to the advocates of the Sunshine Act at least, help reduce the marketing budget as pharmaceutical companies change their practices to enhance their corporate image.

The Sunshine Act applies to all HCPs who receive payments from the drug companies. Thus, payments to investigators in clinical trials will also have to be disclosed, as will payments to members of advisory boards and drug safety monitoring boards. The reasoning behind extending the reporting requirements to clinical research activities is that an HCP who receives payment for marketing activities may also be a principal investigator or a member of an advisory board. Complete transparency is intended to ensure that HCPs do not receive disproportionate remuneration for research activities to compensate for loss of income elsewhere.

To assuage corporate concerns about loss of confidentiality, a delay by up to 4 years will be allowed for disclosure of payments to HCPs involved in the clinical development programme of a new product. But it is the reaction of the HCPs themselves that some find most worrying. The drug industry is currently under very close scrutiny and HCPs will be aware that the general public could take a very negative view of an apparently cosy relationship between drug companies and HCPs and question the independence of the HCPs and their hospitals. In the face of negative public opinion, might those same HCPs reconsider their involvement in research? The potential image problem could be accentuated by disclosure without context. Clinical trials are complex and expensive undertakings (not least because of an increased regulatory burden in recent years), and not all the money will go to lining the pockets of the HCPs. Nevertheless, the public or lay press, in their enthusiasm to expose HCP enrichment at the perceived expense of patients' best interest, may just focus on a lump-sum payment to trial staff, without really caring where that money goes or what clinical research actually involves. Ultimately, this could have a negative impact on research.

In summary, although the intentions of this new disclosure legislation are laudable, and something had to be done to expose the potential conflicts of interest that arise wherever there is a free flow of money from drug companies to HCPs, we should also be aware of possible unintended consequences

(which can often arise when there is an attempt to engineer changes in ingrained behaviour).

### *Regulatory agencies and social media*

When it comes to social media and networking, I must admit that I am rather twentieth century in my outlook – I am happy to use a telephone and e-mail, have a static webpage, and maybe even dabble in LinkedIn, but for the most part the attraction of Twitter<sup>®</sup> has always been beyond me. I could grudgingly admit that *Tweets* from eye witnesses to breaking news stories could also be of interest, but who cares whether Stephen Fry was stuck in a lift for 40 minutes, right? And as for any offerings from the FDA and EMA, who would be interested in *Tweets* from monolithic institutions?

This suspicion of the whole Twitter<sup>®</sup> thing perhaps explains why I took so long to actually investigate the FDA and EMA Twitter<sup>®</sup> feeds (@FDA\_Drug\_Info and @EMA\_News). When I did, I was surprised. In contrast to my prejudice, the *Tweets* were not along the lines of ‘such and such a member of the committee couldn’t make it today because of inclement weather’ but instead read like news announcements. In fact, the

Twitter<sup>®</sup> feeds for the FDA and the EMA (and presumably for most large institutions and companies) are managed by a press department rather than an individual. The downside of this control over output is, I suppose, less spontaneity and you also probably have to be wary of spin. (The FDA in particular is coming up for some refinancing agreements this year and is therefore rather image conscious).

Importantly, when the EMA tweets about, for example, new guidelines for advanced therapies, there is usually a link to the news story on the agency website, which gives more detail than is possible in *Tweets* (which are limited to 140 characters). These news stories then provide a link to the actual guidelines (or whatever the *Tweet* was about). Why, you might ask, can’t you just go to the news sections of the EMA and FDA website? Well yes, of course you can, but I still found that the Twitter<sup>®</sup> format seems excellent at giving you a very succinct overview of what is going on. What is also interesting is that you can quickly see what news stories are generating most attention (as measured by the number of *Retweets*). And this is not to mention the networking potential of Twitter<sup>®</sup> that I have yet to investigate or comprehend.

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## **Indian Government gives green light to cheap Nexavar copy**

In a ruling with major implications, the Controller General of Patents, Designs, and Trade Marks of the Government of India on the 12th of March granted domestic company Natco Pharma a licence to manufacture and sell a generic version of Bayer Corporation’s anticancer drug Nexavar at a knockdown price that ‘shall not exceed (8800 rupees) for a pack of 120 tablets’ (a month’s supply).<sup>1</sup> This represents a massive 97% saving on the current cost of Nexavar (about 280,000 rupees per month).

In arriving at his decision, the Controller General invoked the 1970 Patents Act, according to which any interested party may apply for a compulsory licence after 3 years have expired since the granting of a patent if ‘the reasonable requirements of the public with respect to the patented invention have not been satisfied’.

Natco produced figures, broadly accepted by the Controller General, showing that the amount of Nexavar Bayer imported into India fell way short of what was needed to meet the demand of patients. The Controller General further accepted Natco’s assertion that the drug was unaffordable to the public.

Under the conditions of the licence, Natco must pay a royalty amounting to 6% of net sales to Bayer and provide the product free of charge to ‘atleast (sic) 600 needy and deserving patients per year’.

At the time of writing, Bayer was considering its next move. Keeping its legal team busy is a second case, this one involving Cipla Ltd, which has been selling a generic form of Nexavar in India since 2010. Bayer is currently pursuing the matter through the courts.

While India has modest health expenditure per capita, its population is expected to become the world’s largest within the next few decades.<sup>2</sup>

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## Tamiflu research leaves more publication questions than answers

Tamiflu is the brand name for the drug oseltamivir and is an antiviral used to treat infections caused by viruses, particularly influenza. Tamiflu first came to prominence in the general media in May 2009 after the WHO requested stockpiles of Tamiflu to tackle what it termed a global pandemic of the H1N1 swine flu. This of course had a large impact on sales of Tamiflu, which reached 3.2 billion Swiss Francs in 2009.<sup>1</sup>

The Swiss newspaper, *Neue Zürcher Zeitung*, recently published a very interesting interview with Gerd Antes, director of the German Cochrane Centre.<sup>2</sup> In particular the focus was on the Tamiflu vaccine and the non-publication of research results. Antes notes that over 50% of the results of Tamiflu studies have not been made public, making a proper evaluation of the vaccine nigh on impossible, despite the fact it has been on the market since 1999. The Tamiflu manufacturer counters this accusation saying, 'Roche provided the Cochrane group with access to 3,200 pages of very detailed information, enabling their questions to be answered'.<sup>3</sup>

Critically, Tamiflu's use in a pandemic was evaluated in a 2003 meta-analysis of 10 studies sponsored by Roche.<sup>4</sup> However, of these 10 studies, 8 were unpublished.

Cochrane has been pressing Roche for several years to release all study data and although some information has been forthcoming, the amount of detail remains unsatisfactory to Cochrane, particularly the data relating to side effects. Antes notes that one published study is seven pages long, yet the clinical study report for it is over 2000 pages long.<sup>2</sup> Cochrane suspects a lot of information relating to that study has not been made public.

What role are the authorities playing in all of this? The FDA in the USA sent Roche a warning letter in 2000 instructing Roche to desist from claiming that Tamiflu reduces complications. In order to comply with this until recently Roche ran 2 Tamiflu websites –

one for US residents, and one for the rest of the world (which did not follow the FDA's instruction).

That the European authority (European Medicines Agency (EMA)) came to a different conclusion than the FDA is worrying according to Antes who questions if both authorities were presented with the same information. Dr Fiona Godlee, Editor-in-Chief of the *British Medical Journal*, also picked up on this point and wrote, 'The discrepancies between the conclusions reached by different regulators around the world highlights the absurd situation we find ourselves in. In a globalised world, regulators should cooperate and pool their limited resources. Otherwise we will continue to waste money and risk people's health on drugs that don't work'.<sup>5</sup>

Antes also notes the much better resources at the disposal of the FDA compared to Europe.<sup>2</sup> The FDA employs 170 biostatisticians, a number that European agencies can only dream of.

The Cochrane Collaboration and *BMJ* have been at loggerheads with Roche over full disclosure of Tamiflu results for quite some time. This current spat has been unleashed by the January 2012 issue of *The Cochrane Library* which published an updated Cochrane Review of the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza), antivirals used to treat and prevent influenza.<sup>6</sup>

Of particular interest to EMWA members is the criticism of the role that ghostwriters have played in some of the Tamiflu studies, writing according to Roche's instructions. The *BMJ* has also tackled Roche on this issue in a series of short 'Rapid Responses' and the answers hopefully serve as a barometer to show progress made in the area of ghostwriting over the past decade or so.

Specifically, the *BMJ* alleges that a paper by Treanor *et al.*,<sup>7</sup> published in 2000 in *JAMA* used ghostwriters.<sup>8</sup> Roche's response deserves to be republished in full. 'Roche confirms that medical writers were used to help draft some of the above papers. This is neither unusual nor secretive, and is common practice in the scientific community. At

the time of writing and submission (2002) (*sic*), it was not standard practice for professional medical writers to be named on manuscripts'.<sup>8</sup> Interestingly, this is at odds with the statement by Treanor *et al.*<sup>9</sup> that, 'the pivotal adult treatment trial published in *JAMA* in 2000 was not ghost-written'. The *BMJ* responded, 'While we are prepared to accept Dr Treanor's assurances that he was unaware that his paper was ghostwritten, this of course does not mean that it was not. Roche's evasive answers when asked about this matter only serve to reinforce our concerns'.<sup>8</sup>

Roche further refuted the influence of the marketing department in inserting key messages and had the following to say about ghostwriting at that time. 'During the period of time in question (1999–2002) it was common practice for scientific medical writers to provide writing support for publications with the authors having full access to data and full and final review of the publications. Since the introduction in 2003 of the Good Publication Practice guidelines for Pharmaceutical Companies (GPP), Roche has complied with the practice to acknowledge the involvement of professional medical writers'.<sup>3</sup>

With so many organizations involved and the whole controversy being played out over several years, the Tamiflu publication saga looks set to continue.

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## A new website for reporting and researching drug side effects

David Healy, a professor of psychiatry in Wales, is not much loved by the pharmaceutical industry. EMWA members might remember that he gave a presentation titled 'Ghostwriting: What's the Problem?' at the ICR-EMWA Joint Symposium on Publishing Clinical Trials: Ethics and the Pharmaceutical Industry on 27th February 2008. But what David Healy wants is to make medicines safer for us all – and sometime or other we all become 'patients'. To this end he has founded Data Based Medicine Limited which operates through its website RxISK.org. This is the first free

website (not sponsored by the pharmaceutical industry or advertising) for patients and their doctors to research, and easily report drug side effects. The website is still under construction but states that it will offer a medical timeline chart that captures essential information on treatment-induced problems, tag clouds that help convey the impact of problems on people's lives, and free access to FDA's database of adverse events.

David quotes others when he writes 'the greatest public health benefit would come from getting the greatest number of people on the greatest amount of medications to ward off all conceivable risks' (<http://davidhealy.org/>). He says this target is not

going to work out well. His article on the site titled 'Pills and the Man' explains the obstacles in terms of financial and political interests and concludes that 'It's difficult to avoid the impression that it's the

health of drug companies that regulators and others have been most concerned about'. However, much of your livelihood depends on the industry this article and others on his website give cause for thought.

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## Therapy Limericks, By Graham Guest

I wanted to rapidly fit  
Some new parts to my car bit by bit  
Then I thought of the fact  
While my car was intact  
My infinitive's definitely split  
Prepositions were dear to old Matt  
Whose sentences never were flat  
His rule did not bend  
They'd be put at the end  
So he always knew where they were at

The proofreaders job can be tuff  
When the client's right terrible stuff  
They do just as they pleeze  
Like put two e's in hee's  
When just one e is reely e-nuff

An unknown young fellow called Hound  
Was upset by his name and its sound

He changed it to Getty  
And his girlfriend, Betty  
Said, 'Now you are truly re-nouned'

Clive wanting a life with more glamour  
Established himself as a spammer  
Police came one day  
'What gived me away?'  
'We're afraid, Sir, it was your bad grammar'

*Graham Guest (graham@guest.org.uk) offers coaching for simplicity, grammar coaching, and consulting on the English language, continuing professional development and lifelong learning. He has a background in the management and administration of international professional associations, and experience as a career coach and a psychological counsellor.*

# English Grammar and Style

## Good Writing Practice

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### Pleasing the reader (3)

The fundamental principle in the practice of medicine, 'first, do no harm', could be transposed to the world of medical writing to 'first, do not annoy'. The Good Writing Practice (GWP) group at EMWA has been focussing on our readership and on writing for the reader. We want the reader to want to read what we've written and then appreciate it, so what we must avoid at all costs is causing annoyance. The GWP group came up with a list of writing habits that annoy them. Some of those habits that cause us to bristle come in the category of pet hates and can sometimes be put down to personal taste, whereas others are clearly seen as writing errors.

We've discussed the first impressions a document makes on the reader, and how the document layout, titles and headers contribute to a good first impression. We've highlighted how clearly identifiable mistakes and typos make the reader lose faith in the content of the document, and we've looked at the habit of overwriting, i.e. repeating information unnecessarily or providing excess information.<sup>1</sup>

In this issue, we look at some other sources of annoyance cited by the group.

### Incomprehensible sentences

If the reader doesn't understand what is meant, the writer has failed in the task. The reason for not understanding a sentence might be (a) that it is effectively nonsense, maybe due to a forgotten verb or a misplaced pronoun, (b) that it is too long or convoluted, (c) that certain words are not understandable because they are too long, too specialized (jargon) or have not been explained (abbreviations), or (d) that the sentence is ambiguous. Ambiguity may be caused by a grammatical error, but also by inappropriate punctuation. A slash '/' might mean 'either', 'or' or both of these and if it is interpreted differently by different readers (e.g. by investigators reading instructions in a clinical study protocol) then those readers will record and produce different data. Stephen de Looze wrote a much-quoted article in TWS in 2001 on writing blighted by the slash,<sup>2</sup> and this is well worth a (re)-read. Ambiguous phrases, such as 'within + time period' should be

avoided at all costs,<sup>3</sup> although almost every clinical study protocol I have ever read contains a phrase equivalent to 'within a week of baseline', which can mean either a week before baseline, or a week after baseline, or both. In an effort to clarify, many writers have taken to writing 'within a week prior to baseline', which I don't like (see below under 'Verbosity'), but which is understandable. On the other hand, when that is extended to 'within 4 weeks prior to the first study drug administration' my brain needs a second or two to work out what is meant. Much simpler, more easily understandable solutions are 'in the week before baseline' and 'in the 4 weeks before the first dose'. Any time the reader has to spend re-reading or puzzling over a sentence will cause annoyance at best, but might also lead to the reader giving up completely.

### Patronizing the reader

Avoiding the use of long, involved sentences must not lead to a text that is so simplified that the reader feels patronized. Even a text written for children, such as the patient information in a paediatric study, must take into account the fact that the children reading it are likely to have become experts in their disease. Deciding which abbreviations to spell out in a text must also take into account the readership, but including abbreviations such as *e.g.* and *i.e.* in the list of abbreviations is to my mind always patronizing (like saying 'just in case you didn't have Latin at school'). Unnecessary repetition is patronizing, boring, and leads to confusion because the reader assumes there is something new being said and can't quite understand what. As an editor, how often have you attempted to unravel three paragraphs of text only to discover that everything essential was already contained in the first?

### Verbosity

Even careful medical writers can be prone to verbosity, perhaps because they are too wrapped up in their own writing. The use of long words where a short word would do comes high on my list of annoying habits, for we are not writing novels. I always prefer 'before' to 'prior to', and 'after' to 'following'. The habit of replacing 'than' with

‘compared with’ is rapidly gaining ground, and I increasingly find myself editing it out of texts that come my way. ‘Scores were higher in Group A than in Group B’ – it’s so simple! Why dilute the result by writing ‘Scores were higher in Group A compared with Group B’?

I also do my best to edit the clumsy ‘he/she’ construction out of documents. The sight of a dozen or more of these on a single page of the clinical study protocol makes me wrinkle my nose. The best way to avoid causing such annoyance is to use the plural: *Investigators and their staff are to ensure ... they should ... Patients should be interviewed and their answers recorded ...* Sometimes putting a verb in the imperative can get around the problem: *Record the data directly on the CRF.* Medical writers seem to shy away from this form in a clinical study protocol, possibly because they feel they are writing not only to the investigators, but also to all the reviewers in their company and to health authorities and ethics committees. Anyone who feels very uncomfortable about this might consider writing the imperative as a note: *Note: Record any abnormal findings on page 14 of the CRF.*

## Punctuation

The over or under use of punctuation will irritate some readers no end, while the wrong use of punctuation will cause misunderstanding. The rules of punctuation must always be observed, but much in English punctuation comes down to personal taste. I recently reviewed a CSR written by a contractor, and although I requested a few changes of style, I had no criticism of the punctuation. A colleague (American, but I’m not sure whether that is relevant) who reviewed the same report sent in a review file speckled with red commas. Equally, the overuse of any type of punctuation mark (brackets, dashes, semicolons, exclamation marks), even if used correctly, can lead to annoyance. As medical writers, our job is to look for alternatives to excess punctuation. We are not aiming for literary heights where a sentence covering a third of a page might be exulted as refined composition, we are usually writing to inform. Some of us are rattled by the use of the comma after abbreviations such as *e.g.* and *i.e.* (e.g., like this). What does a comma add here? According to Strunk and White,<sup>4</sup> it is necessary because *e.g.* and *i.e.* are parenthetical. Thankfully, other style guides quite rightly disagree, as they so often do with Strunk and White’s odd claims about the use of English.<sup>5</sup> The English Style Guide issued by the European Commission Directorate-General for Translation<sup>6</sup> instructs its employees to use a comma, colon, or dash before *e.g.* and *i.e.*, but

no comma after them. The Oxford Guide to Style<sup>7</sup> agrees, but tells us that ‘commas are often used in US practice’. Unfortunately, the AMA Manual of Style,<sup>8</sup> which is often taken as the work of reference in medical writing, is one of these US practitioners! Surely a comma after *e.g.* and *i.e.* should come after the entire phrase, for that is the parenthesis: ‘Any OTC pain medication, e.g. paracetamol, should be recorded’ is the same as ‘Any OTC pain medication (e.g. paracetamol) should be recorded’.

## Excessive cross-referencing

In regulatory documents I have the impression that we often over-cross-reference because we err on the side of caution. We fall over ourselves to ensure that the regulatory reviewers find what they want because we don’t want to be accused of not following the templates, or worse, of hiding (unfavourable) results. This attitude is commendable, but can lead to a document littered with cross-references that don’t actually give the reader any further information. No reader wants to be sent off on such a wild goose chase! The rule of thumb should be that if a referenced source does not add any further information, it should be omitted. Hence, in the section presenting the main efficacy results in a Summary of Clinical Efficacy it may be appropriate to cross-reference to the section on subgroup analyses for a particular variable, but it would probably not be useful to do the opposite, because the main efficacy results will not add extra value to the sub-group analyses. Clinical study protocols are often strewn with cross-references, a great many of them to the schedule of assessments. All readers of study protocols should know that the schedule of assessments is always provided and they do not need to be sent to it at every mention of an assessment. One clear reference to it at the beginning of the procedures and variables section should suffice. Lastly, a reference to a reference that then leads to an appendix is guaranteed to annoy. We owe our readers more than that.

## Misspelling

There is really no excuse for misspelling in these days of spell-checkers. We should all be aware of the pitfalls involved in using them (they don’t pick up misspellings if the misspelling is also a legitimate word) but they are a huge aid to those not blessed with good spelling ability. No reader should need to be annoyed by misspellings in a document that has been written on a word-processing system (and any reader who is lucky enough to receive hand-written correspondence these days should



Photograph taken by Neville W. Goodman in the car park of the broadminded Royal United Hospital in Bath, UK.

probably think themselves lucky and excuse a small spelling mistake!).

Awareness of a problem is the first step to resolving it. If we know what annoys us, we are less likely to annoy others. So, the next time you are accused of

being picky, pedantic or particular, take it as a compliment. Medical Writers are by nature all of those and worse, but these traits should be the only sources of annoyance that we cause. The texts we write will be appreciated for their clarity and readability.

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## Points of View

### You can be too careful: When language filtering goes wrong

Subscribers to a UK company's TV service were recently given something to snigger at when unwarranted censorship of programme information left then reading about Charles D\*\*\*ens and Alfred Hitchc\*\*k.<sup>1</sup> The temporary glitch, blamed on new software aimed at filtering out offensive language, also saw the censoring of pop star-turned-radio DJ Jarvis Cocker, London football club Arsenal and even a programme on canals<sup>1</sup>. The title of Will Smith movie Hancock suffered the same fate, although viewers were left disappointed when the film itself was broadcast in full.

This latest incident follows others in which overzealous obscenity filters variously prevented residents of Scunthorpe in the UK from creating accounts with AOL because of the taboo word lurking in their town's name;<sup>2</sup> caused US sprinter Tyson Gay to be referred to as 'Tyson Homosexual' and 'the 25-year-old Homosexual';<sup>3</sup> and resulted in CIA assassination plans being described as 'plots to buttbuttnate foreign leaders'<sup>2,3</sup>.

Long may the problems continue!

## Notes

1. Presumably because 'canal' minus the c = anal.
2. Whoever created the filtering software must have deemed the word 'ass' to be more offensive than 'butt', even when part of a longer, non-backside-related word.

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## Editorial

After a wonderful May spring week in sunny Cyprus – it was good to see so many of you at the Freelance Business Forum (FBF) – it's back to business as usual with a packed issue. The FBF minutes summary has not made it into this issue due to

print deadlines, but we will archive the FBF minutes in the Freelance Resource Centre (FRC) on the EMWA website. Speaking of which, the FRC is fast becoming the useful resource we hoped it would. We invite you to peruse 2012's latest additions – the 'Regulatory Medical Writing' section and the 'Proposal/task order points list'. Both are available to EMWA members only once you are logged in to the EMWA website. These resources have been developed at your request and with the generous support of the following experienced freelancers: Debbie Jordan, Chris Priestley, Andrea Palluch and Claudia Frumento, and of course, your dedicated Freelance Support Team. A huge 'thank you' to all those involved.

Continuing our series of business articles, we bring you insights from Raquel and Linda into how today's volatile currency markets can expose freelancers to business risk.

Bilal recounts his experiences in returning to the UK from Germany as a regulatory medical writer, and his subsequent move into freelancing that has opened new medical communications doors.

Anu's Word Jumbles, complete with Anders' funky illustrations provide our light entertainment – unjumble them to give medical writing-related words; and this issue's 'Toolbox' checks out the currency converter at [www.oanda.com](http://www.oanda.com).

As always, if you'd like to contribute anything at all to OOOO, please do drop us a line. We always love hearing from you!

## Out On One's Own – A Different Perspective

Repatriated British medical writers going OOOO are something of a rarity, because we tend to go abroad and stay there. In my case, however, personal and professional circumstances dictated my return to the UK and my foray into self-employment. Alison McIntosh suggested that I write a piece for OOOO from this perspective, and here is my story, so far.

## A bit about me – My move abroad...and back!

My first role in medical writing was on a 12-month contract as an associate medical writer for Accovion, a medium-sized contract research organisation (CRO) in Eschborn, just outside Frankfurt am Main, Germany. After a steep but highly rewarding learning curve, I moved to what was then Sanofi-Aventis, now Sanofi, in Höchst, where I spent 3 years. My 4 years in Germany were spent exclusively writing regulatory documents, mainly clinical study reports, along with some investigator brochures with contributions to international medicinal product dossiers and investigational new drug applications.

Sanofi wanted to reduce the headcount during their restructuring programme and, with family circumstances calling me home I decided to return to my hometown of Preston once I had the security of a job in Manchester. I worked for a small university spin-off biotechnology company, called Renovo, in Manchester, headed by a University of Manchester professor. We had around 100 staff and were cash-rich through large investments from pharma and venture capitalists. However, our lead drug failed in its pivotal Phase III trial, the results of which came through in February 2011. It was a huge blow to everyone and it meant that we had 3 months to find alternative employment. I had been thinking about going for it alone for a while and thought that it would be a staggered and methodical process. I had already registered my web domain

name 2 months before, and was making tentative steps. However, the speed at which events unfolded over the following few weeks left me flabbergasted. In the space of 3 weeks, I had registered my company, set up a business bank account, registered with an accountancy firm, had a logo developed by a colleague and friend, a website put up by another friend, and had begun phoning for business!

### **Out on one's own, finally!**

My last week of employment was in the middle of June; however, I had already secured work by the end of May, so it was a good start. The end of July right through until the first week of September was crazy where I had a total of 4 days off on the back of working 18-hour days! The rest of September and October, aside 1 week in each were pretty quiet but then business picked up again the day before I flew out to spend a week in Frankfurt with friends in early November, which meant that I essentially had a working holiday! I didn't mind and I love my work, so I made use of my days being productive while my friends were also out to work. December tailed off beautifully before a relaxing holiday in Morocco, and back to the grind in the New Year, with work slowly picking up.

### **Variety truly is the spice of medical writing life!**

I have had the pleasure of undertaking a variety of work from a range of clients. Coming from a regulatory background, companies were hesitant about my lack of experience in medcomms when I was job-hunting to move back to the UK. However, since going OOOO, I have received more medcomms work than regulatory, which has allowed me to showcase and further develop my creative skills. I have learned many new skills and techniques and learned to write a plethora of documents, some of which I had only EMWA training for, or in some cases, hadn't even heard of, e.g. formulary packs! The EMWA medcomms workshops I completed over the years continue to be helpful in allowing me to approach new documents with confidence, and my experience so far has been key to producing

work of the highest quality, enabling me to win repeat business. Becoming acquainted with writing and editing manuscripts, abstracts, posters, power point presentations, review articles, product monographs, and development safety update reports has been a hugely fulfilling experience. For me, the most fun part of my business is the sheer variety of work I undertake, which has enabled me to grow as a writer.

### **Freelancing – there is a market!**

The freelance market, although competitive, has been kind so far. Being a native English speaker with international experience has been a unique selling point for securing business both at home and abroad. Being a fluent German speaker, with intermediate Polish and ever improving French has won me editing work and writing work from pharma companies with international operations. A significant portion of my work has come from medcomms agencies based in the south of England and international CROs; however, I have also won business directly from large pharma and biotech companies abroad.

### **Being my own boss, and thoroughly enjoying it!**

Having my own business and being my own boss was something I had wanted for several years, with various ideas falling short due to funding or life taking a different course. However, going into medical writing has allowed me to realise my initial, albeit evolving, dream. Being my own boss is a liberating experience laced with flexibility: I work when I want, and I don't have anyone aside the tax man to answer to. In tandem with the eclectic mix of projects, I feel vindicated in my decision to go it alone. Of course there are 'troughs', especially this early into my new venture, but they are compensated for by the crazy 'peaks'. So, after a generally successful first 8 months, I am looking forward to an even more successful 2012, wish me luck!

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## **Freelancing and currency exchange problems**

### **Introduction**

Freelancers dealing with clients who operate in other currencies may face the question of how to charge

for their services: should it be in the freelancer's home currency or should it be in the client's currency? Each of these charging strategies has their

pros and cons. The recent economic turmoil and the accompanying volatility in currency exchange put the robustness of these strategies to test.

As part of our business series here at OOOO, we present the experiences of two EMWA members in dealing with different currencies and how it affected their freelance businesses in these times of highly volatile currency fluctuations.

## Strategy one: charging in one's home currency

by Raquel Billiones

My move from Germany to Switzerland in 2006 had several consequences. I went from being an employed medical writer to a start-up freelancer. I left the European Union (and the Eurozone) for a little non-EU country in the Alps. I had to deal with Swiss francs (CHF) and not with euros (EUR) in one of the most expensive cities in the world. And although Switzerland was home to some of the biggest pharma companies, during the first few years of freelancing, my clients were mainly in the Eurozone plus a few in the USA. The question arose about which currency to use when setting my hourly rate, which is usually specified in a general service agreement or freelance work contract. I opted to charge in my home currency and my clients in the Eurozone agreed.

### Upsides

Charging in my home currency (CHF) made a lot of sense. After all, my overheads were all in CHF. I was supposedly 'protected' from the foreign exchange (forex) volatility. This also simplified my bookkeeping/accounting by passing on the job of foreign exchange conversions to the clients. This policy of charging in CHF worked out quite nicely for European clients, especially because of a rather efficient bank transfer system within Europe.

### Downsides

The forex problems of recent years, especially the currency crisis of 2011 brought home the downsides of operating in a stubbornly strong and stable currency such as the CHF.

As early as January 2011, I was told by a potential client that my hourly rate is 'quite expensive' which surprised me because the figure was diligently based on average values reported in the EMWA freelance survey.<sup>1</sup> In 2006, the EUR/CHF average exchange rate was approximately of 1.57.<sup>2</sup>

On 11 August 2011, the EUR/CHF exchange rate reached a record low at 1.0376.<sup>2</sup> With the CHF

almost on par with EUR, my rate suddenly shifted from around the mean to the far right end of the EMWA survey rate range.

To illustrate the extremes in forex volatility, let us take a hypothetical document that I would invoice CHF 10 000 for. In 2006, my client in the Eurozone would need to pay me approximately EUR 6300. On 11 August 2011, the same document would cost the client about EUR 10 000. That was an increase of about 57%.

If my rates suddenly became 'expensive' from the point of view of Eurozone clients, they were atrocious for American clients. When I started out in 2006, the USD/CHF rate was 1.25. On 11 August 2011, it was 0.72.<sup>2</sup> This reversal of fortunes of the two currencies resulted in about 73% increase in my rates from the perspective of the Americans.

In other words, I became one of the most expensive freelance medical writers around without even lifting a finger. In the process, I lost my competitive edge.

I have always been told that long-standing satisfied clients will stick with you through thick and thin and pay a fair price for quality work. Unfortunately, during tough times (and these are tough times), even the most loyal of clients will think of their bottom line first and the long-standing relationship with their service providers only second. The huge increase in the cost of my services would make any client think twice before hiring me for a Eurozone project. For American clients, I was unaffordable.

### Dealing with the problem

*Spread the risks.* The basic advice of 'hedging' one's risks applies to businesses big and small. This entails spreading out the risks among different clients and currencies. If my only source of revenue were clients from outside Switzerland who would balk at paying my CHF rates, I would be in big trouble. However, if 50% of my projects were charged in EUR, in USD or in the client's currency, I would not, theoretically, lose all projects but still be able to keep half. The very few clients I charged in USD were blissfully unaware of my currency problems. Despite a forex loss of more than 40%, at least the projects still kept coming.

*Build up on clients with a common currency.* A business relationship with a client closer to home and with whom I share the same operating currency is less likely to be affected by currency problems. Luckily, I acquired several Swiss clients over the years, clients who are still willing to pay CHF prices for services rendered by Swiss-based

freelancers. Enhancing my business relationship with these clients can definitely pay off in the long run.

*Renegotiate the contract.* I know it is not a good business policy to lower one's rates but when the going gets tough, a talk with a client to renegotiate a contract might be worthwhile. I am not talking about a drastic reduction in hourly rate but rather more about a temporary arrangement, such as a currency adjustment discount (or something similar) which can easily be cancelled once the currency problems are (hopefully) resolved. The arrangement should, of course, be fair to both parties. A satisfied client would be amenable to shouldering some of the loss to keep a reliable and valued service provider. I will lose some money in the process but at least I get to keep the project, the client and the good business relationship. At times like this, the main objective should not be about maximising revenue but minimising loss.

*Find a more stable source of income.* The currency instability led me to consider employment once again. I approached a Swiss client and landed a part-time regulatory writing job and a stable source of income in my home currency. The trade-off was to give up all regulatory freelance projects but I still get to keep my freelance editing and web-based media projects.

## Strategy two: charging in the client's currency

by Linda Liem

A few years ago, I moved from the Netherlands, a European Union country using the EUR, to Norway, a country outside the EU with its own currency, the Norwegian krone (NOK). Although I now had to use the NOK for my expenses and not the EUR, I never put much thought into the way I charged my clients for my work.

I started as a freelance medical writer before we moved to Norway and had already established a client base. Not all of them followed me, but enough did which allowed me to continue writing without a lot of acquisition effort. As I was already charging my clients in EUR, I felt that changing the currency that I used would not help my relationship with my existing clients. Some clients worked within tight budgeting regulations, where differences between budgeted and final expenses were strongly discouraged. Others needed my projected costs as accurately as possible, as they had to account for this in their proposals to their clients.

The NOK is not a major currency in the world, so it was questionable that my clients would accept the

NOK instead of the Euro without discussion. I didn't think that changing my currency to the NOK was worth the hassle that would in all probability arise with my clients.

### Upsides

The main advantage of the way I deal with different currencies is that it is client friendly. It ensures that my clients will not get an unexpected financial surprise between the acceptance of a project and the final invoice. The price of the project is not affected by currency fluctuations and will stay the same throughout.

This approach also ensures that I can deal with all my clients the same way, whether they are based in Europe or the USA. All get proposals in their own currency and none have to deal with exchange rate fluctuations. To make sure that I would earn the same amount per hour in NOK, I adapted the base rate per hour I use for my proposals according to the exchange rate. So my hourly rate in USD is higher than in EUR, because the EUR is stronger than the USD.

### Downsides

The burden of accounting for conversion rates and exchange variations lies on my shoulders. With a strong home currency, like the NOK now is, there is a risk of earning less than expected. Luckily, my freelance activities are not my only sources of income. When doing research for this article, it occurred to me that I might have to adjust my base rates again, as the exchange rates have shifted quite a lot lately.

My financial administration has also become more complicated. The Norwegian bookkeeping regulations for small businesses are much more stringent and bureaucratic than the Dutch. I even bought a bookkeeping programme to help me with my administration, which is a pain to use but does comply with Norwegian legislation. Unfortunately, as expensive as the programme and the mandatory service level agreement are, they can only process NOK. If I want functionality for different currencies, I have to buy their enterprise edition, which is not realistic at all for a freelance writer like me!

In my bookkeeping, I have to account for exchange rate differences between my invoices (which are in the client's currency) and payments received (in NOK). I convert the invoices myself with the help of an online currency converter when I enter them in NOK in the system. I use the OANDA currency converter<sup>2</sup> because it's easy to use and you can easily get the exchange rate for a

date different than today. When my client has paid me, I enter the actual amount in NOK and book the difference as exchange rate loss or gain. I'm still on the lookout for an easier system, but haven't found another tool yet that is easier to use and adapted for Norway.

### *Dealing with the problem*

The world is in turmoil and is going to stay that way for the foreseeable future. The best you can do is to spread the risk across clients and currencies. In addition, you should cherish your relationship with your existing customers and diversify your activities.

*Cherish your relationship with your clients.* I work mainly with existing clients and my relationship with them is one of the most important assets I have. Keeping them happy ensures that they come back with more work. It also makes them more willing to discuss the price for a proposal, as they know me and the way I work. It works both ways. Remember that your client saves on the effort and uncertainty of finding a competent contractor, because they have you!

*Diversify.* It's important to keep an open eye for opportunities that may work for you, even if they do not immediately fit your medical writing description. Finding a part-time job earns you some money, while allowing you to keep up with your medical writing activities. Looking for projects in neighbouring fields, e.g. editing or journalism, gives you an opportunity to learn and broaden your experience.

In the past few years, I worked as a teacher and as an external hire for the wages department in our municipality. Now, I lead a project to leverage and develop the Ritland Crater, a recently discovered meteorite crater in our neighbouring municipality. In all these jobs, as diverse as they are, I found

ample opportunities to learn, to develop myself, and earn some money too. Although these are quite extreme examples of diversification, there may be other opportunities that can help you to make it through these difficult times.

*Know your strategy.* In the end, it's up to you to determine what you're willing to accept. Are you willing to renegotiate your rates to keep clients? Do you want to look further for projects outside your comfort zone? Even if you don't have currency exchange problems, it may be harder to find clients or projects. Don't wait until you get stuck in a corner, but prepare yourself by thinking about what you're willing to do, what other potential opportunities you have and where your limits lie. That way, you will have control over your decisions, no matter what the future brings.

## Conclusion

We hope that in the longer term, the currency market normalises. Unfortunately, at the time of writing, the light at the end of the tunnel is barely visible. And even if the currency market eventually stabilises, other crashes in the future cannot be ruled out.

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## References

1. Reeves A, Hamilton S. EMWA Freelance Business Survey. *The Write Stuff* 2007;16:138-140.
2. OANDA® currency converter ([www.oanda.com](http://www.oanda.com)). See also a review of the currency converter in *The Toolbox* on page xx.

# Medical Writing Jumble # 3

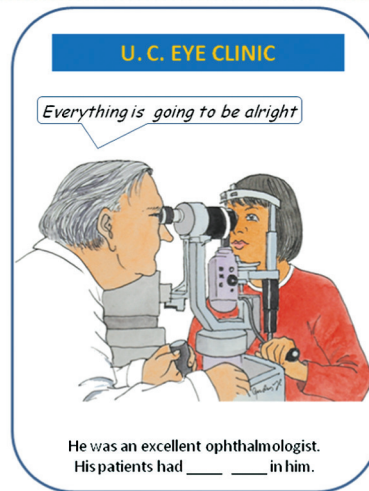
1. Rearrange the jumbled letters to get a meaningful word related to medical writing.
2. Next, take the circled letters from each word and make two new words that will answer the riddle in the cartoon. Hint: The answer is probably a pun.
3. Use British English.

GIRUFE   

HEATD   

KABNL   

LAMINA   



**Answer:**           

by Anuradha Alahari | Illustration: Anders Holmqvist

See page 188 for the answers.

## The tool box

Oanda® Currency Converter



Five years ago, during a teleconference with a potential client, I was asked to quote my hourly rate and I was silly enough to blurt it out in my local currency (Swiss franc, CHF). My second mistake was not being sufficiently prepared to

## Historical Exchange Rates

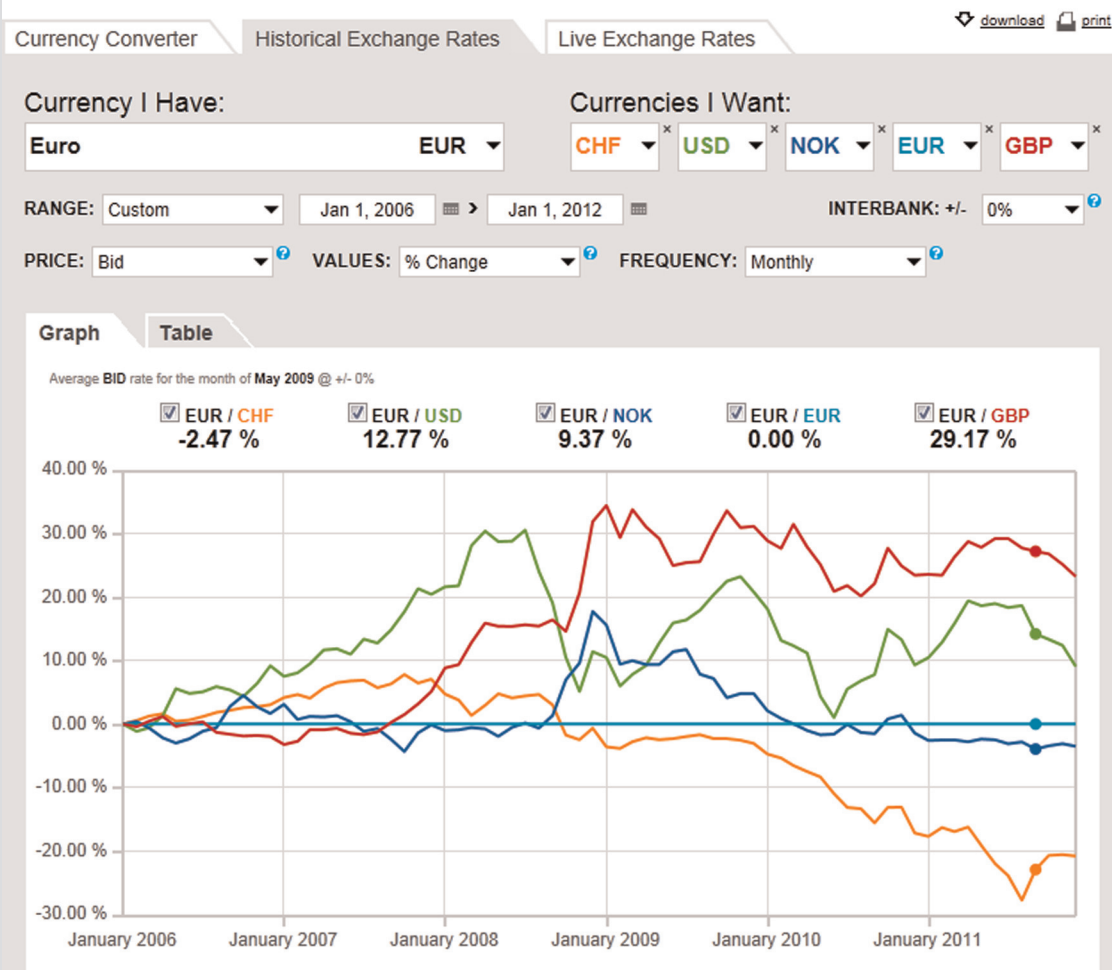


Figure 1: Currency volatility (% change) from January 2006 to January 2012.

EUR/CHF						CHF/EUR					
Interbank Rate +/- 0%						Interbank Rate +/- 0%					
Jan 1, 2012						Jan 1, 2012					
EUR	CHF	EUR	CHF	EUR	CHF	CHF	EUR	CHF	EUR	CHF	EUR
1	1.22	15	18.25	45	54.74	1	0.82	15	12.32	45	36.96
2	2.43	20	24.33	50	60.83	2	1.64	20	16.43	50	41.07
3	3.65	25	30.41	100	121.66	3	2.46	25	20.53	100	82.13
4	4.87	30	36.50	250	304.14	4	3.29	30	24.64	250	205.33
5	6.08	35	42.58	500	608.28	5	4.11	35	28.75	500	410.66
10	12.17	40	48.66	1,000	1,216.55	10	8.21	40	32.85	1,000	821.32

Figure 2: Traveller's cheatsheet.

answer the question ‘how much is that in American dollars?’ Anyway, I learned my lesson and that’s how I found the OANDA® currency converter.

OANDA® is designed for finance professionals and therefore provides a wide range of foreign exchange trade tools which may be free or charged. But even small business owners like me can find free currency tools at OANDA® which are easy to use and available in different languages. This review covers only those features which I personally used and found useful.

### Historical exchange rates

The OANDA® currency converter offers info on current (‘live’) as well as historical exchange rates. The live info is nice to have but it is the historical info that is a must-have for me, especially when doing my book-keeping. As an example, I updated my books in preparation for my 2011 tax declaration and so I needed to know how much the EMWA conference in Berlin in May 2011 (charged in EUR) cost in CHF. That’s where OANDA® helped me.

The historical feature comes in handy in finding back exchange rates from months or even years before. OANDA® boasts of currency exchange rates data that go back to January 1990.

Input:

- I enter the currency I have (base currency) and define the currency(ies) I want to convert to (up to five currencies).
- I give a time period (‘date range’ of from – to).
- I define the values I want – rate or % change.
- I define the data frequency to be displayed (daily, weekly, etc.)

Output:

- I can view the results in a tabular or graphic format (Fig. 1).
- In the tabular view, in addition to individual data points, the period average (mean), period high (max), and period low (min) rates are also displayed.



Figure 3: Mobile currency converter on a smartphone.

### Traveler’s cheatsheet

Another nice-to-have tool is a personalised credit card-sized printable ‘cheat-sheet’ for quick and easy currency conversion. This is especially useful when travelling or when speaking with potential clients (Fig. 2).

### Mobile currency converter

If you are the paperless 3G-phone type, a OANDA® mobile currency converter (‘app’) is available for iPhone®, BlackBerry®, and Android® (Fig. 3).

### Other currency exchange tools

There are, of course, other currency converters available online. XE® currency converter (www.xe.com) has quite a following in the UK.

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FIGURE, DEATH, BLANK, and ANIMAL.  
 He was an excellent ophthalmologist. His  
 patients had BLIND FAITH in him.